# CONTENTS

## General, physical, and inorganic


| NO. | | PAGE |
|---|---|---|
| 108 | Studies in co-ordination chemistry. Part XV. Complexes of chromium with a di(tertiary arsine)<br>By R. S. NYHOLM and G. J. SUTTON | 560 |
| 109 | Studies in co-ordination chemistry. Part XVI. Complexes of bivalent and tervalent manganese with a di(tertiary arsine)<br>By R. S. NYHOLM and G. J. SUTTON | 564 |
| 110 | Studies in co-ordination chemistry. Part XVII. Complexes of ruthenium with a di(tertiary arsine)<br>By R. S. NYHOLM and G. J. SUTTON | 567 |
| 111 | Studies in co-ordination chemistry. Part XVIII. Complexes of osmium with a di(tertiary arsine)<br>By R. S. NYHOLM and G. J. SUTTON | 572 |
| 117 | The reaction of methyldisiloxanes and 1 : 1-dimethyldisilthiane with boron and hydrogen halides<br>By H. J. EMELÉUS and M. ONYSZCHUK | 604 |
| 118 | Preparation and properties of dimethyliodosilane, 1 : 1′ : 2 : 2′-tetramethyl-disiloxane and -disilthiane<br>By H. J. EMELÉUS and L. E. SMYTHE | 609 |
| 119 | Complex fluorides of quadrivalent osmium and iridium and the corresponding free acids<br>By M. A. HEPWORTH, P. L. ROBINSON, and G. J. WESTLAND | 611 |
| 121 | Physical properties of the lower dialkyl hydrogen phosphites<br>By F. M. PAGE and J. H. PURNELL | 621 |
| 129 | The kinetics of the oxidation of ethane by nitrous oxide<br>By R. KENWRIGHT, P. L. ROBINSON, and A. B. TRENWITH | 660 |
| 130 | Solutions in sulphuric acid. Part XXIV. Electrical conductivity, cryoscopic, and density measurements on solutions in dideuterosulphuric acid<br>By R. H. FLOWERS, R. J. GILLESPIE, J. V. OUBRIDGE, and C. SOLOMONS | 667 |
| 139 | Raman spectra of the tetraiodogallate ($GaI_4^-$) and tetraiodoindate ($InI_4^-$) ions in aqueous solution<br>By L. A. WOODWARD and G. H. SINGER | 716 |
| 140 | Tetrahedral nickel(II) complexes and the factors determining their formation. Part I. Bistriphenylphosphinenickel(II) compounds<br>By L. M. VENANZI | 719 |
| 145 | Antimony halides as solvents. Part I. Cryoscopic data in antimony trichloride<br>By G. B. PORTER and E. C. BAUGHAN | 744 |
| 146 | Reactions of tin(IV) halides with ammonia derivatives. Part I. The reaction of tin(IV) chloride with liquid ammonia<br>By E. BANNISTER and G. W. A. FOWLES | 751 |
| 164 | Studies in co-ordination chemistry. Part III. The thermodynamics of interaction between heterocyclic bases and (diacetyl bisbenzoylhydrazone)nickel(II) in benzene<br>By L. SACCONI, G. LOMBARDO, and P. PAOLETTI | 848 |
| 171 | A nuclear magnetic resonance study of the hydrates of molybdenum trioxide<br>By S. MARIČIĆ and J. A. S. SMITH | 886 |

NOTE

| | | |
|---|---|---|
| 180 | Thermogravimetric analysis of ammonium phosphomolybdate *in vacuo*<br>By S. J. GREGG and R. STOCK | 910 |


XUM

NO. PAGE

## Physical organic

105 Mesomorphism and chemical constitution. Part X. The 2-*p*-*n*-alkoxybenzylideneaminophenanthrenes and evidence for the planarity of the diphenyl ring system in the mesomorphic state
By G. W. GRAY . . . . . 552

123 Mechanism and stereochemistry of the addition of nitrogen dioxide to olefins
By J. C. D. BRAND and I. D. R. STEVENS . . . . . 629

131 The tautomerism of *N*-heteroaromatic hydroxy-compounds. Part III. Ionisation constants
By S. F. MASON . . . . . 674

135 Physicochemical studies on starches. Part IX. The mechanism of the β-amylolysis of amylose and the nature of the β-limit dextrin
By J. M. G. COWIE, I. D. FLEMING, C. T. GREENWOOD, and D. J. MANNERS . . 697

136 Physicochemical studies on starches. Part X. The molecular weight of the water-soluble polysaccharides of sweet corn, *Zea mays*
By C. T. GREENWOOD and P. C. DAS GUPTA . . . . . 703

137 Physicochemical studies on starches. Part XI. The granular starch of sweet corn, *Zea mays*
By C. T. GREENWOOD and P. C. DAS GUPTA . . . . . 707

138 Physicochemical studies on starches. Part XII. The molecular weight of glycogens in aqueous solution
By W. A. J. BRYCE, C. T. GREENWOOD, I. G. JONES, and D. J. MANNERS . . 711

149 Chemical and infrared spectral evidence for the structure of thiocyanogen trichloride
By R. G. R. BACON, R. S. IRWIN, J. McC. POLLOCK, and A. D. E. PULLIN . . 764

150 Thiocyanogen chloride. Part I. Chemical evidence for the existence of the monomeric compound in solutions in organic solvents
By A. B. ANGUS and R. G. R. BACON . . . . . 774

151 Thiocyanogen chloride. Part II. Some physical properties of its solutions
By R. G. R. BACON and R. S. IRWIN . . . . . 778

152 An infrared spectroscopic examination of some anhydrous sodium soaps
By D. CHAPMAN . . . . . 784

153 Reactions of organic azides. Part VIII. Kinetics of the rearrangement of 9-azidofluorene in sulphuric–acetic acid
By C. L. ARCUS and J. V. EVANS . . . . . 789

157 The ionic dissociation and reactivity of some arylmethyl chlorides
By S. F. MASON . . . . . 808

169 Entropy changes in isomerisations
By R. M. GASCOIGNE . . . . . 876

## Organic

103 Sugar nitrates. Part IV. Reactions of nitrates and sulphonates with sodium methoxide in methanol and some sodium salts
By JOHN HONEYMAN and THEO. C. STENING . . . . . 537

104 Nucleotides. Part XLIII. The use of cyanamide derivatives in pyrophosphate synthesis. Syntheses of $P^1$-adenosine-5′ $P^2$-uridine-5′ pyrophosphate and of cytidine-5′ pyrophosphate
By G. W. KENNER, C. B. REESE, and SIR ALEXANDER TODD . . . . . 546

106 Chaksine. Part I
By AHMAD KAMAL and GEORG HAHN . . . . . 555

107 Alicyclic diketones and diols. Part I. *cis*- and *trans*-2 : 2 : 5 : 5-Tetramethyl*cyclo*hexane-1 : 3-diol.
By A. W. ALLAN, R. P. A. SNEEDEN, and (in part) J. COLVIN . . . . . 557

112 Rearrangements of some *cyclo*octatetraene derivatives
By C. R. GANELLIN and R. PETTIT . . . . . 576

113 The reaction between aromatic compounds and derivatives of tertiary acids. Part X Elimination of carbon monoxide from some highly alkylated acetyl chlorides
By MICHAEL E. GRUNDY, WEI-HWA HSÜ, and EUGENE ROTHSTEIN . . . . 581

| No. | | Page |
|---|---|---|
| 114 | Quantitative aspects of the acid reversion of glucose<br>By Stanley Peat, W. J. Whelan, T. E. Edwards, and (Mrs.) O. Owen. | 586 |
| 115 | The constitution of larch ε-galactan<br>By G. O. Aspinall, E. L. Hirst, and Else Ramstad | 593 |
| 116 | Immunopolysaccharides. Part VIII. Enzymic synthesis of 6-*O*-α-D-glucopyranosyl-3-*O*-methyl-D-glucose by *Betacoccus arabinosaceous*<br>By S. A. Barker, E. J. Bourne, P. M. Grant, and M. Stacey | 601 |
| 120 | Cyclic amidines. Part VI. 5- and 7-Substituted 2-amino-4-hydroxyquinolines<br>By R. Hardman and M. W. Partridge | 614 |
| 122 | Studies in the synthesis of terpenes. Part III. The synthesis of 6-acetoxy-5 : 5 : 9-trimethyl-*trans*-decal-1-one<br>By B. Gaspert, T. G. Halsall, and D. Willis | 624 |
| 124 | Cereal gums. Part III. The constitution of an araboxylan from barley flour<br>By G. O. Aspinall and R. J. Ferrier | 638 |
| 125 | Metal derivatives of conjugated dienes. Part I. Butadiene- and *cyclo*hexadiene-iron tricarbonyls<br>By B. F. Hallam and P. L. Pauson | 642 |
| 126 | Ferrocene derivatives. Part IV. Indenyl- and tetrahydroindenyl-iron carbonyls<br>By B. F. Hallam and P. L. Pauson | 646 |
| 127 | Ferrocene derivatives. Part V. Ferrocenealdehyde<br>By G. D. Broadhead, J. M. Osgerby, and P. L. Pauson | 650 |
| 128 | Ferrocene derivatives. Part VI. DL-Ferrocenylalanine.<br>By J. M. Osgerby and P. L. Pauson | 656 |
| 132 | Fungicidal activity and chemical constitution. Part V. Synthesis of some substituted quinolines<br>By D. Woodcock and (Miss) V. W. Rogers | 685 |
| 133 | Photochemical transformations. Part III. The constitution of a steroid irradiation product<br>By D. H. R. Barton and A. S. Kende | 688 |
| 134 | Ferrocene derivatives. Part VII. Some sulphur derivatives<br>By G. R. Knox and P. L. Pauson | 692 |
| 141 | The structure of laminarin. Part I. The main polymeric linkage<br>By Stanley Peat, W. J. Whelan, and H. G. Lawley | 724 |
| 142 | The structure of laminarin. Part II. The minor structural features<br>By Stanley Peat, W. J. Whelan, and H. G. Lawley | 729 |
| 143 | Carcinogenic nitrogen compounds. Part XXIV. The synthesis of indole and quinoline compounds from cyclic ketones<br>By Ng. Ph. Buu-Hoï, P. Jacquignon, and T. B. Loc | 738 |
| 144 | The synthesis of some galactaric (mucic) acid derivatives<br>By K. Butler, D. R. Lawrance, and M. Stacey | 740 |
| 147 | The chemistry of bacteria. Part VII. The structure of violacein<br>By J. A. Ballantine, C. B. Barrett, R. J. S. Beer, Stephen Eardley, Alexander Robertson, B. L. Shaw, and T. H. Simpson | 755 |
| 148 | Infrared absorption of NMe and $NMe_2$ groups in amines<br>By R. D. Hill and G. D. Meakins | 760 |
| 154 | The structure of ruscogenin<br>By D. Burn, B. Ellis, and V. Petrow | 795 |
| 155 | Modified steroid hormones. Part VIII. Some 16-bromo- and 16-chloro-derivatives of testosterone<br>By B. Ellis, D. Patel, and V. Petrow | 800 |
| 156 | Potential anti-purines. Part I. The synthesis of derivatives of 8-thiapurine (2-thia-1 : 3 : 4 : 6-tetra-azaindene) by a new reaction<br>By G. M. Timmis | 804 |
| 158 | The reaction of ninhydrin with cyclic α-imino-acids<br>By A. W. Johnson and D. J. McCaldin | 817 |
| 159 | Cyclodehydration processes. Part I. Benzofuran derivatives formed by cyclisation of ω-aryloxyacetophenones<br>By W. Davies and S. Middleton | 822 |


XUM

| NO. | | PAGE |
|---|---|---|
| 160 | The nitration product of 3 : 4-dihydro-4-methyl-3-oxo-4 : 7-phenanthroline<br>By W. O. SYKES | 825 |
| 161 | A search for new trypanocides. Part V. Some derivatives of 10-phenyl-4 : 9-diazaphenanthrene<br>By M. DAVIS | 828 |
| 162 | Calciferol and its relatives. Part III. Partial synthesis of calciferol and of *epi*-calciferol<br>By I. T. HARRISON and B. LYTHGOE | 837 |
| 163 | Calciferol and its relatives. Part IV. A non-photochemical synthesis of a model *cis*-triene<br>By I. T. HARRISON and B. LYTHGOE | 843 |
| 165 | The alkylation of mercaptobenzothiazole<br>By K. J. MORGAN | 854 |
| 166 | The oxidation of derivatives of *o*-phenylenediamine. Part V. $N^3$-Substituted derivatives of anilino*apos*afranine (rimino-compounds) and related compounds<br>By VINCENT C. BARRY, J. G. BELTON, J. F. O'SULLIVAN, and DERMOT TWOMEY | 859 |
| 167 | Electrolytic reduction of some αβ-unsaturated steroid ketones<br>By PETER BLADON, J. W. CORNFORTH, and (MRS) R. H. JAEGER | 863 |
| 168 | Fluorocarbohydrates. Part I. The synthesis of 6-deoxy-6-fluoro-α-D-galactose and 5-deoxy-5-fluoro-αβ-D-ribose<br>By N. F. TAYLOR and P. W. KENT | 872 |
| 170 | Triterpenes of the friedelane series. Part III. The course of the friedelene–oleanene rearrangement<br>By J. L. COURTNEY, R. M. GASCOIGNE, and A. Z. SZUMER | 881 |
| 172 | The relative stabilising influences of substituents on free alkyl radicals. Part IV. Selective hydrogen-abstraction by free *tert.*-butoxy-radicals<br>By R. L. HUANG and SURINDER SINGH | 891 |
| 173 | The tautomerism and steric properties of 9-substituted phenanthridines<br>By C. B. REESE | 895 |

NOTES

| | | |
|---|---|---|
| 174 | The reaction of 9-chlorophenanthridine and related compounds with tertiary amines<br>By C. B. REESE | 899 |
| 175 | Some anilinoquinones and *N*-substituted 2-hydroxy-1 : 4-naphthaquinone imines<br>By M. Z. BARAKAT, S. K. SHEHAB, and M. M. EL-SADR | 901 |
| 176 | Researches on polyenes. Part VI. The synthesis of *trans*-1-2′-phenanthrylbuta-1 : 3-diene<br>By B. B. MILLWARD and M. C. WHITING | 903 |
| 177 | A synthesis of 3-*O*-β-D-galactopyranosyl-D-galactose<br>By D. H. BALL and J. K. N. JONES | 905 |
| 178 | Search for chemotherapeutic amidines. Part XV. 2-Methoxy- and 2-hydroxy-derivatives of 1 : 5-di-*p*-aminophenoxypentane<br>By M. DAVIS | 907 |
| 179 | Certain reactions of 4-methoxydiphenyl<br>By W. H. LINNELL and H. J. SMITH | 908 |
| 181 | *cyclo*Hexane-1 : 3-diones. Part III. Alkaline hydrolysis of ethyl 2 : 4-dioxo-6-styryl*cyclo*hexanecarboxylate<br>By G. R. AMES and W. DAVEY | 911 |
| 182 | Action of acidic reagents on 2 : 4 : 5-trimethoxybenzyl and 2-methoxy-4 : 5-methylenedioxybenzyl alcohol<br>By T. R. GOVINDACHARI, K. NAGARAJAN, and P. C. PARTHASARATHY | 912 |
| 183 | Polynuclear heterocyclic systems. Part XII. Further examples of the Elbs reaction with heterocyclic ketones<br>By G. M. BADGER and B. J. CHRISTIE | 913 |
| 184 | Ethoxide–hydroxide-ion competition in bimolecular nucleophilic substitutions in alkaline aqueous ethyl alcohol<br>By Y. POCKER | 915 |

# INDEX OF AUTHORS' NAMES


ALLAN, A. W., Sneeden, R. P. A., and Colvin, J., 557
Ames, G. R., and Davey, W., 911
Angus, A. B., and Bacon, R. G. R., 774
Arcus, C. L., and Evans, J. V., 789
Aspinall, G. O., and Ferrier, R. J., 638
Aspinall, G. O., Hirst, E. L., and Ramstad, E., 593
Bacon, R. G. R., and Irwin, R. S., 778
Bacon, R. G. R., Irwin, R. S., Pollock, J. McC., and Pullin, A. D. E., 764
Bacon, R. G. R. See also Angus, A. B., 774
Badger, G. M., and Christie, B. J., 913
Ball, D. H., and Jones, J. K. N., 905
Ballantine, J. A., Barrett, C. B., Beer, R. J. S., Eardley, S., Robertson, A., Shaw, B. L., and Simpson, T. H., 755
Bannister, E., and Fowles, G. W. A., 751
Barakat, M. Z., Shehab, S. K., and El-Sadr, M. M., 901
Barker, S. A., Bourne, E. J., Grant, P. M., and Stacey, M., 601
Barrett, C. B. See Ballantine, J. A., 755
Barry, V. C., Belton, J. G., O'Sullivan, J. F., and Twomey, D., 859
Barton, D. H. R., and Kende, A. S., 688
Baughan, E. C. See Porter, G. B., 744
Beer, R. J. S. See Ballantine, J. A., 755
Belton, J. G. See Barry, V. C., 859
Bladon, P., Cornforth, J. W., and Jaeger, R. H., 863
Bourne, E. J. See Barker, S. A., 601
Brand, J. C. D., and Stevens, I. D. R., 629
Broadhead, G. D., Osgerby, J. M., and Pauson, P. L., 650
Bryce, W. A. J., Greenwood, C. T., Jones, I. G., and Manners, D. J., 711
Burn, D., Ellis, B., and Petrow, V., 795
Butler, K., Lawrance, D. R., and Stacey, M., 740
Buu-Hoï, Ng. Ph., Jacquignon, P., and Loc, T. B., 738
Chapman, D., 784
Christie, B. J. See Badger, G. M., 913
Colvin, J. See Allan, A. W., 557
Cornforth, J. W. See Bladon, P., 863
Courtney, J. L., Gascoigne, R. M., and Szumer, A. Z., 881
Cowie, J. M. G., Fleming, I. D., Greenwood, C. T., and Manners, D. J., 697
Das Gupta, P. C. See Greenwood, C. T., 703, 707
Davey, W. See Ames, G. R., 911
Davies, W., and Middleton, S., 822
Davis, M., 828, 907
Eardley, S. See Ballantine, J. A., 755
Edwards, T. E. See Peat, S., 586
Ellis, B., Patel, D., and Petrow, V., 800
Ellis, B. See also Burn, D., 795
El-Sadr, M. M. See Barakat, M. Z., 901
Emeléus, H. J., and Onyszchuk, M., 604
Emeléus, H. J., and Smythe, L. E., 609
Evans, J. V. See Arcus, C. L., 789
Ferrier, R. J. See Aspinall, G. O., 638
Fleming, I. D. See Cowie, J. M. G., 697
Flowers, R. H., Gillespie, R. J., Oubridge, J. V., and Solomons, C., 667
Fowles, G. W. A. See Bannister, E., 751
Ganellin, C. R., and Pettit, R., 576
Gascoigne, R. M., 876
Gascoigne, R. M. See also Courtney, J. L., 881
Gaspert, B., Halsall, T. G., and Willis, D., 624
Gillespie, R. J. See Flowers, R. H., 667
Govindachari, T. R., Nagarajan, K., and Partha-sarathy, P. C., 912
Grant, E. J. See Barker, S. A., 601
Gray, G. W., 552
Greenwood, C. T., and Das Gupta, P. C., 703, 707
Greenwood, C. T. See also Bryce, W. A. J., 711, and Cowie, J. M. G., 697
Gregg, S. J., and Stock, R., 910
Grundy, M. E., Wei-Hwa Hsü, and Rothstein, E., 581
Hahn, G. See Kamal, A., 555
Hallam, B. F., and Pauson, P. L., 642, 646
Halsall, T. G. See Gaspert, B., 624
Hardman, R., and Partridge, M. W., 614
Harrison, I. T., and Lythgoe, B., 837, 843
Hepworth, M. A., Robinson, P. L., and Westland, G. J., 611
Hill, R. D., and Meakins, G. D., 760
Hirst, E. L. See Aspinall, G. O., 593
Honeyman, J., and Stening, T. C., 537
Huang, R. L., and Singh, S., 891
Irwin, R. S. See Bacon, R. G. R., 764, 778
Jacquignon, P. See Buu-Hoï, Ng. Ph., 738
Jaeger, R. H. See Bladon, P., 863
Johnson, A. W., and McCaldin, D. J., 817
Jones, I. G. See Bryce, W. A. J., 711
Jones, J. K. N. See Ball, D. H., 905
Kamal, A., and Hahn, G., 555
Kende, A. S. See Barton, D. H. R., 688
Kenner, G. W., Reese, C. B., and Todd, Sir A., 546
Kent, P. W. See Taylor, N. F., 872
Kenwright, R., Robinson, P. L., and Trenwith, A. B., 660
Knox, G. R., and Pauson, P. L., 692
Lawley, H. G. See Peat, S., 724, 729
Lawrance, D. R. See Butler, K., 740
Linnell, W. H., and Smith, H. J., 908
Loc, T. B. See Buu-Hoï, Ng. Ph., 738
Lombardo, G. See Sacconi, L., 848
Lythgoe, B. See Harrison, I. T., 837, 843
McCaldin, D. J. See Johnson, A. W., 817
Manners, D. J. See Bryce, W. A. J., 711, and Cowie, J. M. G., 697
Maričić, S., and Smith, J. A. S., 886
Mason, S. F., 674, 808
Meakins, G. D. See Hill, R. D., 760
Middleton, S. See Davies, W., 822
Millward, B. B., and Whiting, M. C., 903
Morgan, K. J., 854
Nagarajan, K. See Govindachari, T. R., 912
Nyholm, R. S., and Sutton, G. J., 560, 564, 567, 572
Onyszchuk, M. See Emeléus, H. J., 604
Osgerby, J. M., and Pauson, P. L., 656
Osgerby, J. M. See also Broadhead, G. D., 650
O'Sullivan, J. F. See Barry, V. C., 859
Oubridge, J. V. See Flowers, R. H., 667
Owen, O. See Peat, S., 586
Page, F. M., and Purnell, J. H., 621
Paoletti, P. See Sacconi, L., 848
Parthasarathy, P. C. See Govindachari, T. R., 912
Partridge, M. W. See Hardman, R., 614
Patel, D. See Ellis, B., 800
Pauson, P. L. See Broadhead, G. D., 650, Hallam, B. F., 642, 646, Knox, G. R., 692, and Osgerby, J. M., 656

Peat, S., Whelan, W. J., Edwards, T. E., and Owen, O., 586
Peat, S., Whelan, W. J., and Lawley, H. G., 724, 729
Petrow, V. See Burn, D., 795, and Ellis, B., 800
Pettit, R. See Ganellin, C. R., 576
Pocker, Y., 915
Pollock, J. McC. See Bacon, R. G. R., 764
Porter, G. B., and Baughan, E. C., 744
Pullin, A. D. E. See Bacon, R. G. R., 764
Purnell, J. H. See Page, F. M., 621
Ramstad, E. See Aspinall, G. O., 593
Reese, C. B., 895, 899
Reese, C. B. See also Kenner, G. W., 546
Robertson, A. See Ballantine, J. A., 755
Robinson, P. L. See Hepworth, M. A., 611, and Kenwright, R., 660
Rogers, V. W. See Woodcock, D., 685
Rothstein, E. See Grundy, M. E., 581
Sacconi, L., Lombardo, G., and Paoletti, P., 848
Shaw, B. L. See Ballantine, J. A., 755
Shehab, S. K. See Barakat, M. Z., 901
Simpson, T. H. See Ballantine, J. A., 755
Singer, G. H. See Woodward, L. A., 716
Singh, S. See Huang, R. L., 891
Smith, H. J. See Linnell, W. H., 908
Smith, J. A. S. See Maričić, S., 886
Smythe, L. E. See Emeléus, H. J., 609
Sneeden, R. P. A. See Allan, A. W., 557
Solomons, C. See Flowers, R. H., 667
Stacey, M. See Barker, S. A., 601, and Butler, K., 740
Stening, T. C. See Honeyman, J., 537
Stevens, I. D. R. See Brand, J. C. D., 629
Stock, R. See Gregg, S. J., 910
Sutton, G. J. See Nyholm, R. S., 560, 564, 567, 572
Sykes, W. O., 825
Szumer, A. Z. See Courtney, J. L., 881
Taylor, N. F., and Kent, P. W., 872
Timmis, G. M., 804
Todd, Sir A. See Kenner, G. W., 546
Trenwith, A. B. See Kenwright, R., 660
Twomey, D. See Barry, V. C., 859
Venanzi, L. M., 719
Wei-Hwa Hsü. See Grundy, M. E., 581
Westland, G. J. See Hepworth, M. A., 611
Whelan, W. J. See Peat, S., 586, 724, 729
Whiting, M. C. See Millward, B. B., 903
Willis, D. See Gaspert, B., 624
Woodcock, D., and Rogers, V. W., 685
Woodward, L. A., and Singer, G. H., 716

XUM

# PAPERS ACCEPTED

The unsaturation and tautomeric mobility of heterocyclic compounds. Part XII. The methylation of 6 : 4′-disubstituted and 4′-substituted 2-anilinobenzothiazoles. By R. F. HUNTER, E. R. PARKEN, and EILEEN M. SHORT

Problems involved in the polarography of triphenyltetrazolium chloride. By B. JAMBÓR

Trypanocides of the phenanthridine series. Part II. Pyrimidinylphenanthridines. By T. I. WATKINS

Differential capacity measurements in aqueous and methanolic ammonium chloride, ammonium fluoride, and hydrochloric acid solutions in relation to anion adsorption. By A. A. MOUSSA, H. M. SAMMOUR, and H. A. CHALY

Molecular polarisability. The anisotropies of seven monosubstituted benzenes and of nitromethane as solutes in carbon tetrachloride. By R. J. W. LE FÈVRE and B. PURNACHANDRA RAO

First-order calculation of factor group splittings in the electronic spectra of durene, coronene, ovalene, and phthalocyanine crystals. By L. E. LYONS

Dephenylation reactions of phenylboron acids and esters. By E. W. ABEL, W. GERRARD, and M. F. LAPPERT

The hydroxylation of some αβ-unsaturated ketones by molecular oxygen. By R. HOWE and F. J. MCQUILLIN

Organic fluorine compounds. Part V. The instability of some sodium 1 : 1-di-*H*-perfluoroalkoxides and its effect on the yields of fluoroethers. By E. J. P. FEAR, J. THROWER, and J. VEITCH

Polymerizations of ethylene in the presence of titanium tetrachloride and certain metal alkyls. By J. C. MCGOWAN and B. M. FORD

Peroxides of elements other than carbon. Part I. The preparation and reactions of peroxysilanes. By E. BUNCEL and ALWYN G. DAVIES

Some constituents of the broad bean. By M. T. J. ABBOT, JOHN FREDERICK GROVE, and P. MCCLOSKEY

Studies in hydrogen-bond formation. Part VII. Reactions between carbohydrates and proteins in water, and their relation to certain biological phenomena. By I. C. L. BRUCE, C. H. GILES, and S. K. JAIN

Molecular polarisability. The specific Kerr constants and polarisations of various polystyrenes dissolved in carbon tetrachloride. By (MRS.) C. G. LE FÈVRE, R. J. W. LE FÈVRE, and (MISS) G. M. PARKINS

The reactivity of esters of quinquevalent phosphorus towards anions. By R. F. HUDSON and D. C. HARPER

Nitrous acid equilibria in perchloric acid. By T. A. TURNEY and G. A. WRIGHT

The reactions of ethylthioethyl *OO*-dimethyl phosphorothioates in water. By D. F. HEATH

The conductivity of silver salts in non-aqueous and mixed solvents. Part VI. By V. S. GRIFFITHS and M. L. PEARCE

The kinetics and mechanisms of aromatic halogen substitution. Part VI. Some observations relating to substitution *meta-* to principally *ortho–para*-directing substituents; and to steric inhibition of tautomeric electron release from the acetamido-group. By P. B. D. DE LA MARE and M. HASSAN

Substitution reactions in the trisethylenediaminecobalt(III) ion. By J. A. FRIEND and E. K. NUNN

The infrared spectra of the methylsilyl halides and related compounds. By E. A. V. EBSWORTH, M. ONYSZCHUCK, and N. SHEPPARD

Aromatic alkylation. Part I. The kinetics of the acid-catalysed aralkylation by diarylmethanols in acetic acid solution. By D. BETHELL and V. GOLD

Indicator measurements in solutions of hydrochloric acid in acetic acid. By D. P. N. SATCHELL

Indicator measurements in the solvent systems $ZnCl_2$–$CH_3CO_2H$ and $ZnCl_2$–HCl–$CH_3CO_2H$. By D. BETHELL, V. GOLD, and D. P. N. SATCHELL

The kinetics of hydrogen-isotope exchange reactions. Part VII. Aromatic hydrogen exchange in the solvent systems $ZnCl_2$–$CH_3CO_2H$ and $ZnCl_2$–HCl–$CH_3CO_2H$. By D. P. N. SATCHELL

Aromatic alkylation. Part II. Diarylmethylation reactions in the solvent systems $ZnCl_2$–$CH_3CO_2H$ and $ZnCl_2$–HCl–$CH_3CO_2H$. By D. BETHELL and V. GOLD

The kinetics of the hydrolysis of methylene dichloride. By I. FELLS and E. A. MOELWYN-HUGHES

XUM

The kinetics of alkaline hydrolysis of substituted ethyl 1-naphthoates. By A. FISCHER, W. J. MITCHELL, G. S. OGILVIE, J. PACKER, J. E. PACKER, and J. VAUGHAN

Vibrational frequency correlations in heterocyclic molecules. Part IV. Indoxyl derivatives. By S. J. HOLT, A. E. KELLIE, D. G. O'SULLIVAN, and P. W. SADLER

Phospholipids. Part III. The hydrolysis of the *cis*- and the *trans*-isomer of glycerol 1-(2-hydroxy*cyclo*hexyl phosphate) and related compounds. By D. M. BROWN, G. E. HALL, and (MISS) H. M. HIGSON

Calculations of the crystal spectra of benzene and naphthalene. By D. P. CRAIG and J. R. WALSH

The reactivity of some active nucleophilic reagents with organophosphorus anticholinesterases. By A. L. GREEN, G. L. SAINSBURY, B. SAVILLE, and M. STANSFIELD

The effect of the salt $Ph_3CSnCl_5$ on the stannic chloride-catalysed polymerisation of styrene. By T. G. BONNER, J. M. CLAYTON, and (the late) GWYN WILLIAMS

The depolymerisation of paraldehyde in the solvent system zinc chloride–acetic acid. By D. P. N. SATCHELL

The chemistry of hop constituents Part XII. The structure of humulinone. By G. A. HOWARD and C. A. SLATER

Potential trypanocides. The action of polymethylene dihalides on 4-aminoquinaldine. By W. C. AUSTIN, M. D. POTTER, and R. P. TAYLOR

Chelate derivatives of trimethylplatinum. By A. K. CHATTERJEE, R. C. MENZIES, J. R. STEEL, and F. N. YOUDALE

Acid catalysis of glycol fission by lead tetra-acetate. By R. P. BELL, V. C. RIVLIN, and WILLIAM A. WATERS

The crystal and molecular structure of tetraethylammonium iodide. By E. WAIT and H. M. POWELL

An addition compound of tetraethylammonium bromide and succinimide. By H. M. POWELL and E. WAIT

A synthesis of coproporphyrin III. By E. BULLOCK, A. W. JOHNSON, E. MARKHAM, and K. B. SHAW

The preparation of tetramethylammonium hydrogen dichloride and the structure of the hydrogen dichloride ion. By T. C. WADDINGTON

*cis*- and *trans*-2 : 3-Dichlorohexafluorobut-2-ene. By F. DICKINSON, R. HILL, and J. MURAY

Extrusion of sulphur. Part III. Polycyclic 1 : 4-thiazepines. By R. H. B. GAIT, J. D. LOUDON, and A. D. B. SLOAN

The relative affinities of an amine, an organic phosphine, and a sulphide for cadmium ion. By STEN AHRLAND, J. CHATT, N. R. DAVIES, and A. A. WILLIAMS

Synthesis of 2α-methylcholest-4-en-3-one. By J. A. K. QUARTEY

The preparation of 7- and 9-glucopyranosyl and -xylopyranosyl derivatives of 8-azaxanthine (6 : 8-dihydroxy-1 : 2 : 3-triazolo[4,5-*d*]pyrimidine). By J. BADDILEY, J. G. BUCHANAN, and G. O. OSBORNE

Syntheses in the colchicine series. Part II. Some tricyclic models. By H. J. E. LOEWENTHAL

Cyclisations with hydrazine. Part I. The preparation of phenanthrene compounds and of pyrene from aldehydes. A variation in reductions of the Wolff–Kishner type. By R. G. R. BACON and W. S. LINDSAY

Cyclisations with hydrazine. Part II. Conversion of 2 : 2′-diacyldiphenyls into compounds of the phenanthrene and 4 : 5-6 : 7-dibenzo-1 : 2-diazocine series. By R. G. R. BACON and W. S. LINDSAY

The synthesis of 2-*N*-alkylcarbamoyl*cyclo*pentanones. By DAVID H. JOHNSON

*N*-Oxides and related compounds. Part XI. Mononitration of 2-, 3-, and 4-phenyl- and 2- and 4-benzyl-pyridine 1-oxide. By A. R. HANDS and A. R. KATRITZKY

5-Alkyl-1 : 2-benzacridines. Synthesis of 5-methyl-1 : 2-benzacridine. By A. CAMPBELL and E. N. MORGAN

The synthesis of some substituted hexahydro-12-methyl-2-oxophenanthrenes. By F. H. HOWELL and D. A. H. TAYLOR

Addition compounds of gallium trichloride. Part V. Ionic 1 : 1 and 1 : 2 complexes with pyridine. By N. N. GREENWOOD and K. WADE

Addition compounds of gallium trichloride. Part VI. Complexes with piperidine. By N. N. GREENWOOD and K. WADE

The constitution of yohimbine and related alkaloids. Part X. The synthesis of some 12*H*-indolo[2 : 3-*a*]pyridocolinium salts, including flavocoryline and flavopereirine. By K. B. PRASAD and G. A. SWAN

The constitution of yohimbine and related alkaloids. Part XI. A synthesis of sempervirine. By G. A. SWAN

XUM

The constitution of yohimbine and related alkaloids. Part XII. Some unsuccessful synthetic approaches to yohimbine and alstoniline. By K. B. PRASAD and G. A. SWAN
Stereoisomeric 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydro-1-hydroxypyridocolines. By G. A. SWAN
Dodecylquinolinium bromide. By A. V. FEW, A. R. GILBY, R. H. OTTEWILL, and H. C. PARREIRA
The reaction between ammonia and transition-metal halides. Part IV. The reaction of ammonia with vanadium(IV) chloride. By G. W. A. FOWLES, and D. NICHOLLS
Modified steroid hormones. Part IX. The 2- and 4-chloro-derivatives of 17β-propionoxyandrosta-1 : 4-dien-3-one and -1 : 4 : 6-trien-3-one. By DAVID N. KIRK and VLADIMIR PETROW
Preparation and hydrolysis of some derivatives of 1 : 3 : 4-thiadiazole. By V. PETROW, O. STEPHENSON, A. J. THOMAS, and A. M. WILD
The synthesis of indolo(2′ : 3′-1 : 2)- and indolo(3′ : 2′-1 : 2)-carbazole. By FREDERICK G. MANN and TREVOR J. WILLCOX
Preparation of cortisol acetate and 21-acetoxy-17α-hydroxypregna-4 : 9-diene-3 : 20-dione from 5α-steroids. By R. M. EVANS, G. F. H. GREEN, J. S. HUNT, A. G. LONG, B. MOONEY, and G. H. PHILLIPPS
Phenylation with diazoaminobenzenes. By R. L. HARDIE and R. H. THOMSON
5-Alkylacridines. Part II. Dialkylaminoalkylacridines. By N. FISHER, C. S. FRANKLIN, E. N. MORGAN, and D. J. TIVEY
1 : 2-Benzocoronene and naphtho(2′ : 3′-1 : 2)coronene. By E. CLAR and M. ZANDER
Methyl ethers of L-fucose. By J. G. GARDINER and ELIZABETH PERCIVAL
The synthesis of the *v*-triazolo[*d*]pyrimidine analogues of adenosine, inosine, guanosine, and xanthosine, and a new synthesis of guanosine. J. DAVOLL
Synthesis of fluoranthenes. Part XIII. Synthesis of benzo(1 : 2-*a*, 3 : 4-*a*′)diacenaphthylene and of benzo(1 : 2-*a*, 4 : 5-*a*′)diacenaphthylene. By S. HORWOOD TUCKER
Nucleotides. Part XLIV. Thymidine-5′ pyrophosphate and thymidine-5′ triphosphate. By (MRS.) B. E. GRIFFIN and SIR ALEXANDER TODD
Application of the Bruckner method to the synthesis of phenanthridine derivatives. Part II. By T. R. GOVINDACHARI, B. R. PAI, and V. N. SUNDARARAJAN
Chlorophyll and related compounds. Part VII. The structure of bacteriochlorophyll. By J. H. GOLDEN, R. P. LINSTEAD, and G. H. WHITHAM
1 : 2-Dicarboxylic acids. Part IV. The α-ethyl α′-methyl succinic acids and their derivatives. By J. H. GOLDEN and R. P. LINSTEAD
The use of adsorption for isolation of aromatic substances. By A. ASATOOR and C. E. DALGLIESH
Florisil as an adsorbent for basic substances. By A. ASATOOR and C. E. DALGLIESH
The dimer of *O*-benzoquinone. By JOHN HARLEY-MASON and A. H. LAIRD
*Solanum* alkaloids. Part XIII. The examination of the alkaloids from seven *Solanum* species. By LINDSAY H. BRIGGS and R. C. CAMBIE
Decamethylene dibromide. By E. P. TAYLOR
Preparation of ketones by cleavage of 2 : 4-dinitrophenylhydrazones. By N. M. CULLINANE and B. F. R. EDWARDS
A short synthesis of 3-methylfuran. By J. W. CORNFORTH
Tocopherols. Part I. Synthesis of 7-methyltocol (*n*-tocopherol). By D. MCHALE, P. MAMALIS, J. GREEN, and S. MARCINKIEWICZ
The chemical synthesis of polysaccharides. Part II. The chemical synthesis of nigerose. By S. HAQ and W. J. WHELAN
The synthesis of 1-aryl arsindolines. By EMRYS R. H. JONES and FREDERICK G. MANN
Improved preparation of intermediates for the synthesis of α-aminobutyric acids. Derivatives having functional γ-substituents. By Y. KNOBLER and MAX FRANKEL
Synthesis of DL-canaline and some of its derivatives. By Y. KNOBLER and MAX FRANKEL
Synthetic experiments in the *cyclo*heptatrienone series. Part VII. By R. S. COFFEY and A. W. JOHNSON
Quinolizines. Part I. Synthesis of some indole[2,3-*a*]quinolizine and benz[*g*]indolo[2,3-*a*]-quinolizine derivatives. By E. E. GLOVER and GURNOS JONES
Thiophen derivatives. Part XI. Substitution in 2-thenaldehyde. By NG. PH. BUU-HOÏ and DENISE LAVIT
Electrical conduction in fused gallium dichloride and gallium dibromide. By N. N. GREENWOOD and I. J. WORRALL
Reactions of ammonia with nickel(II) cyanide. By E. E. AYNSLEY and W. A. CAMPBELL
The kinetics of the base-catalysed decomposition of benzyl *tert.*-butyl peroxide. By R. P. BELL and A. O. MCDOUGALL

XUM

## 103. *Sugar Nitrates. Part IV.* Reactions of Nitrates and Sulphonates with Sodium Methoxide in Methanol and Some Sodium Salts.*

By John Honeyman and Theo. C. Stening.

Treatment with sodium methoxide of the 3-nitrate and 3-toluene-*p*-sulphonate of 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose and the 6-nitrate and 6-toluene-*p*-sulphonate of 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose yielded the corresponding alcohols, although with the nitrates much decomposition occurred. Removal of nitrate groups with sodium nitrite in aqueous ethanol has been studied and the stability of sulphonates towards this reagent has been demonstrated. Methyl 4-*O*-methyl-β-D-glucoside has been obtained by preferential removal of the 4-nitrate group of methyl β-D-glucoside 2 : 3 : 4 : 6-tetranitrate. The stability of nitrate groups towards acids has been confirmed by preparation of methyl 2-*O*-methyl-α-D-glucoside 3-nitrate from its 4 : 6-*O*-benzylidene derivative and by removal of the 5 : 6-*cyclo*hexylidene group from 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-nitrate.

Some new nitrates have been prepared in the glucose and galactose series by the action of fuming nitric acid in acetic anhydride on the parent alcohol [1] or by treatment of the corresponding 6-deoxy-6-iodo-sugar with silver nitrate in boiling methyl cyanide. The relative stability of nitrate groups to acid hydrolysis is shown by the preparation in good yield of methyl 2-*O*-methyl-α-D-glucoside 3-nitrate from its 4 : 6-*O*-benzylidene derivative, and that of 1 : 2-*O*-*cyclo*hexylidene-D-glucose 3-nitrate from the corresponding 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-nitrate. Selective nitration of methyl 4 : 6-*O*-benzylidene-α-D-glucoside gave the 3-nitrate in 28% yield.

Reaction of 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-toluene-*p*-sulphonate with sodium methoxide in boiling methanol gave 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose (94%). Similar reaction of the corresponding 3-nitrate proceeded with much decomposition to give the same product (69%) together with nitrite ion (34%) and nitrate ion (42%). Sodium (1·49 equivalents) was used in the reaction, and no unsaturated compounds could be detected in the organic products. When 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose was boiled with sodium methoxide in methanol, the amount of sodium methoxide present decreased and *cyclo*hexanone was formed in small amounts.

Removal of the nitrate group from 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-nitrate may occur by (1) nucleophilic attack by methoxide ion on the nitrogen atom, yielding parent alcohol and methyl nitrate, (2) nucleophilic attack by methoxide ion on the carbon atom, giving a methyl ether and nitrate ion, (3) elimination of a β-hydrogen atom with formation of an unsaturated derivative and nitrate ion, or (4) elimination of an α-hydrogen atom, yielding a carbonyl group and nitrite ion. The use of anhydrous methanol in this de-esterification prevents reactions involving hydroxyl ion: formation of an anhydro-ring is not possible in this blocked ester. Only mechanism (1) yields the parent alcohol; our results showed that 69% of the reaction occurred in this way and 31% by other routes. No methyl ethers have been encountered in this or similar work, eliminating mechanism (2), and the absence of unsaturated compounds shows that mechanism (3) does not occur to a measurable extent. That ether formation can occur in such reactions has been shown by the formation of methyl β-D-glucoside from tetra-*O*-acetyl-α-D-glucosyl nitrate,[2] and of 2-ethoxyoctane from 1-methylheptyl nitrate.[3] Only mechanism (4) gives rise to nitrite; the quantity of nitrite present in our reaction mixture was in agreement with the value of

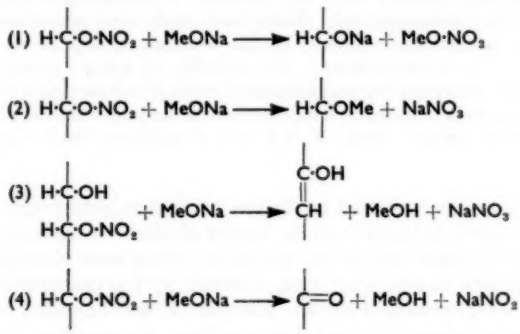
* Part III, *J.*, 1957, 2278.

[1] Honeyman and Morgan, *Chem. and Ind.*, 1953, 1035.
[2] Gladding and Purves, *J. Amer. Chem. Soc.*, 1944, **66**, 76.
[3] Cristol, Franzus, and Shadan, *ibid.*, 1955, **77**, 2512.



XUM

31% suggested for this possibility. No ketonic product was isolated, but the quinoxaline derivative from methyl 4 : 6-*O*-benzylidene-α-D-glucoside was obtained by adding *o*-phenylenediamine after treatment of the 2 : 3-dinitrate with sodium methoxide in methanol,[4] proving the formation of ketonic products in these reactions. Nitrate ion could be formed by the alkaline hydrolysis of methyl nitrate. Although the presence of this nitrate was not proved, only 76% of the nitrogen present could be accounted for, and Shepherd [5] observed that in the hydrolysis products of methyl β-D-glucoside 2 : 3 : 4 : 6-tetranitrate at least 0·45 mol. of nitrate was present in non-ionic form. In both mechanisms (1) and (4) nitrogen–oxygen bond fission takes place: inversion at the carbon atom is not observed. It is therefore suggested that the ketonic product is degraded, consuming additional alkali.




Under similar conditions, the 6-nitrate and 6-toluene-*p*-sulphonate of 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose gave the parent alcohol in good yield: no methyl ethers were isolated. Alkaline hydrolysis of 1 : 2-3 : 5-di-*O*-*iso*propylidene-D-glucose 6-toluene-*p*-sulphonate is reported [6] to give some 5 : 6-didehydro-6-deoxy-1 : 2-3 : 5-di-*O*-*iso*propylidene-D-glucose, but no unsaturated derivatives could be detected in the reactions of the 6-nitrate and 6-toluene-*p*-sulphonate used in the present work. Thus the ester groups were being removed mainly by a mechanism analogous to (1), but the presence of a small quantity of nitrite in the case of the 6-nitrate indicated that some reaction was occurring by a mechanism analogous to (4).

It may be concluded from these and earlier results that a 6-nitrate group is removed from an aldohexose by sodium methoxide with nitrogen–oxygen cleavage only, giving mainly the parent alcohol together with some aldehyde. If formation of an anhydro-ring is possible, however, the reaction proceeds by carbon–oxygen fission only, giving the anhydro-ring. A nitrate group on a secondary carbon atom is removed with nitrogen–oxygen fission unless an anhydro-ring can be formed, in which case the nitrate group may be removed partly by nitrogen–oxygen fission to give the parent alcohol and ketonic products, and partly by carbon–oxygen fission with inversion to give an anhydro-compound. These two types of fission may occur simultaneously in the case of a nitrate group attached to a secondary carbon atom when anhydro-ring formation is possible, but only one type occurs in the case of a similar primary nitrate group. In the first case a ditoluene-*p*-sulphonate gives the anhydro-ring only whereas a diacetate gives the diol, and in this respect the nitrate group is intermediate between an acetate and a sulphonate group. As the nitrate group attracts electrons less strongly than a toluene-*p*-sulphonate group, it is to be expected that it will form anhydro-rings less readily. However, these fundamental reactions of the nitrate group are complicated by conformational effects, and by side

[4] Honeyman and Morgan, *J.*, 1955, 3660.
[5] Shepherd, *J.*, 1953, 3635.
[6] Ohle and von Vargha, *Ber.*, 1929, **62**, 2425.

XUM

reactions and degradations which increase with the number of nitrate groups in the molecule and often predominate.

A mechanism was suggested earlier [4] for removal of nitrate groups by sodium iodide. This was confirmed when methyl 4 : 6-*O*-benzylidene-3-deoxy-3-iodo-α-D-glucoside was heated with sodium iodide in acetone for 4 days at 100°. Starting compound was recovered (75%), but when heating was for only 20 hr. the corresponding 3-nitrate was converted in 21% yield into methyl 4 : 6-*O*-benzylidene-α-D-glucoside.[4] It follows that the latter reaction is unlikely to proceed through the 3-deoxy-3-iodo-derivative. Newth has reported [7] that methyl 4 : 6-*O*-benzylidene-3-deoxy-3-iodo-α-D-glucoside 2-toluene-*p*-sulphonate gives the corresponding 2 : 3-didehydro-2 : 3-dideoxy-derivative when heated with sodium iodide for only 10 min. This reaction does not occur when the 2-hydroxyl group is unsubstituted, even if the time of heating is increased 500-fold, thus exhibiting a similar effect to that observed by Foster and Overend [8] for 1 : 2-diols. This reagent attacked 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-nitrate slowly, 59% of nitrate being removed in 48 hr. at 100°. The corresponding 3-toluene-*p*-sulphonate and methyl β-L-arabinoside 2 : 3 : 4-tritoluene-*p*-sulphonate were recovered unchanged when treated similarly, confirming the stability of sulphonyl groups attached to secondary carbon atoms in the sugar-ring towards this reagent. Boiling 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose 6-nitrate with sodium iodide in *iso*butyl methyl ketone for 2 days gave the 6-deoxy-6-iodo-derivative: the prolonged boiling required is another example of the stability of 6-esters of 1 : 2-3 : 4-di-*O*-*iso*propyliene-D-galactose.[9]

Reduction of a primary toluene-*p*-sulphonate group with lithium aluminium hydride results in a terminal methyl group,[10,11] but similar reduction of 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose 6-nitrate has now been found to give the parent alcohol as when a nitrate group is attached to a secondary carbon atom.[12] It should be noted that a secondary toluene-*p*-sulphonyloxy-group gives mainly the free hydroxyl group under such conditions (in contrast to a primary sulphonate), but sometimes a deoxy-sugar is obtained.[13,14]

Our study of reactions of sodium nitrite in aqueous ethanol [4,15,16] has been continued. When methyl 4 : 6-*O*-benzylidene-α-D-glucoside 3-nitrate was boiled with the reagent for 7 days, the products were unchanged compound (52%) and the glucoside (15%), showing the stability of the 3-nitrate group. Treatment of the 2 : 3-dinitrate for only 21 hr. had given [4] the 3-nitrate in 70% yield, so it was possible that in this case the 3-nitrate group was activating that on $C_{(2)}$. Any ester group with a positively charged centre atom, as in the nitrate group, should have a similar activating effect on an adjacent nitrate group, and that this was true for the methanesulphonate group was shown when methyl 4 : 6-*O*-benzylidene-α-D-glucoside 2-methanesulphonate 3-nitrate was boiled with the reagent for 21 hr.: the 3-nitrate group was removed (42%), giving methyl 4 : 6-*O*-benzylidene-α-D-glucoside 2-methanesulphonate, together with starting compound (41%). That a 2-nitrate group is stable when not adjacent to another nitrate group was shown by boiling methyl 4 : 6-*O*-benzylidene-α-D-glucoside 2-nitrate with the reagent for 21 hr., for it was recovered substantially unchanged (51%). When 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-nitrate was boiled with sodium nitrite in aqueous ethanol for 3 days, the nitrate group was removed slowly, to give 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose (31%) and starting compound (48%). The slow removal of the nitrate group by this reagent and by sodium iodide is probably due to the absence of a suitable activating group.

[7] Newth, *J.*, 1956, 471.
[8] Foster and Overend, *J.*, 1951, 2452.
[9] Tipson, *Adv. Carbohydrate Chem.*, 1953, **8**, 185.
[10] Schmid and Karrer, *Helv. Chim. Acta*, 1949, **32**, 1371.
[11] Karrer and Boettcher, *Chem. Ber.*, 1953, **36**, 571.
[12] Ansell and Honeyman, *J.*, 1952, 2778.
[13] Allerton and Overend, *J.*, 1954, 3629.
[14] Vis and Karrer, *Helv. Chim. Acta*, 1954, **37**, 378.
[15] Ennor, Honeyman, and Stening, *Chem. and Ind.*, 1956, 1308.
[16] Honeyman and Stening, *J.*, 1957, 2278.

Sodium nitrite in aqueous ethanol reacts slowly with a 6-nitrate group, to give the parent alcohol, and in this respect the reaction is different from that with sodium iodide which gives the 6-deoxy-6-iodo-sugar. Methyl 2 : 3 : 4-tri-*O*-acetyl-α-D-glucoside 6-nitrate was recovered (62%) after being boiled with the reagent for 18 hr., and 3 : 5-*O*-benzylidene-1 : 2-*O*-*iso*propylidene-D-glucose 6-nitrate gave the parent alcohol (34%) and starting compound (52%). Similar treatment of 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose 6-nitrate for 7 days gave the alcohol (4%) and starting compound (78%), a further example of the stability of such galactose derivatives. The use of this reagent to prepare partially methylated sugars was demonstrated by the preparation of methyl 4-*O*-methyl-β-D-glucoside. Methyl β-D-glucoside 2 : 3 : 4 : 6-tetranitrate was boiled with sodium nitrite in aqueous ethanol for 5·5 hr., and the resultant methyl β-D-glucoside 2 : 3 : 6-trinitrate was methylated; reduction of the nitrated methyl ether with zinc and iron dust in glacial acetic acid gave methyl 4-*O*-methyl-β-D-glucoside; the overall yield from methyl β-D-glucoside is 24%, and the preparation involves 4 stages, whereas by previous methods [17,18] the compound is obtained in 7% and 12% yield in preparations involving 7 stages. These denitrations are not caused by the weak alkaline solution which results when sodium nitrite is dissolved in water, for high yields of products are obtained, and no inversion or anhydro-ring formation can be detected even after prolonged boiling. Nitrate groups are removed more slowly by sodium nitrite in anhydrous ethanol, owing to the lower solubility of sodium nitrite. Solvent action is negligible, for methyl 4 : 6-*O*-benzylidene-α-D-glucoside 2 : 3-dinitrate was recovered (75%) after being boiled in aqueous alcohol for 4 days. Sulphonates are stable to the reagent, further evidence that alkaline hydrolysis is not the cause of removal of the nitrate group. The 2 : 3-ditoluene-*p*-sulphonate and 2 : 3-dimethanesulphonate of methyl 4 : 6-*O*-benzylidene-α-D-glucoside, methyl 3 : 4-*O*-*iso*propylidene-β-L-arabinoside 2-toluene-*p*-sulphonate, methyl β-L-arabinoside 2 : 3 : 4-tritoluene-*p*-sulphonate, and 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose 6-toluene-*p*-sulphonate were all recovered in high yield after being boiled with aqueous ethanolic sodium nitrite for 2—5 days, showing the stability of such groups towards the reagent. Methyl 4 : 6-*O*-benzylidene-α-D-glucoside 2 : 3-diacetate was deacetylated (79%) after similar treatment for 7 days: the diacetate was recovered after being boiled alone in the solvent for a similar period. Hence the deacetylation by sodium nitrite is probably due to the alkaline solution.

Sodium nitrate in boiling aqueous ethanol did not react with methyl 4 : 6-*O*-benzylidene-α-D-glucoside 2 : 3-dinitrate, but similar treatment of this compound with sodium acetate for 7 days gave unchanged compound (42%) and 3-nitrate (27%). When treated similarly for 5 days, 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-nitrate gave a small quantity of parent alcohol, but starting compound (87%) was recovered. When boiled with sodium carbonate in aqueous ethanol, nitrate groups were removed by alkaline hydrolysis with much decomposition.

## Experimental

The petroleum used was light petroleum, b. p. 60—80°; chloroform solutions were dried over sodium sulphate before being evaporated under reduced pressure; chromatographic separations were carried out by passing dried solutions through activated alumina, Type H 100/200S mesh, supplied by Messrs. Peter Spence and Sons Ltd.

Where appropriate, identity was established by methods including determination of mixed m. p.s.

Unless otherwise stated $[\alpha]_D$ are in chloroform.

*Preparation of Nitrates.*—(a) 1 : 2-5 : 6-*Di*-O-iso*propylidene-D-glucose 3-nitrate.* Acetic anhydride (5 ml.) containing fuming nitric acid (2 ml.) was added to 1 : 2-5 : 6-di-*O*-*iso*propylidene-D-glucose (4 g.) suspended in acetic anhydride (10 ml.) at 0°, and after 25 min. at room temperature the solution was poured into ice-water containing potassium carbonate. The

[17] McGilvray, *J.*, 1952, 3648.
[18] Hayward and Purves, *Canad. J. Chem.*, 1954, **32**, 19.

syrup, washed repeatedly with ice-water, was extracted with chloroform, and the extract was chromatographed. Evaporation of the chloroform eluant gave 1 : 2-5 : 6-*di*-O-iso*propylidene*-D-*glucose* 3-*nitrate*, a syrup (3·26 g.), $[\alpha]_D^{21}$ −40·4° (*c* 5·5) (Found: C, 47·1; H, 6·3; N, 4·7. $C_{12}H_{19}O_8N$ requires C, 47·2; H, 6·3; N, 4·6%).

(b) 1 : 2-5 : 6-*Di*-O-cyclo*hexylidene*-D-*glucose* 3-*nitrate*. Similar treatment of 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose [19] (8 g.) yielded, when the reaction solution was poured into ice-water, a white solid which, recrystallised from methanol, was 1 : 2-5 : 6-*di*-O-cyclo*hexylidene*-D-*glucose* 3-*nitrate* (6·52 g., 73%), m. p. 83—84°, $[\alpha]_D^{20}$ −22·2° (*c* 0·9) (Found: C, 56·4; H, 7·1; N, 3·5. $C_{18}H_{27}O_8N$ requires C, 56·2; H, 7·1; N, 3·6%).

(c) 1 : 2-3 : 4-*Di*-O-iso*propylidene*-D-*galactose* 6-*nitrate*. Fuming nitric acid (3 ml.) in acetic anhydride (7 ml.) was added at 0° to a solution of 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose [20] (14 g.) in acetic anhydride (35 ml.). After 20 min. at room temperature, the mixture, when treated by the procedure described for 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-nitrate, yielded a product which, recrystallised from aqueous ethanol, was 1 : 2-3 : 4-*di*-O-iso*propylidene*-D-*galactose* 6-*nitrate* (11·4 g., 69%), m. p. 61°, $[\alpha]_D^{19\cdot5}$ −59·8° (*c* 2·0) (Found: C, 47·5; H, 6·1; N, 4·3. $C_{12}H_{19}O_8N$ requires C, 47·2; H, 6·3; N, 4·6%).

(d) 3 : 5-O-*Benzylidene*-1 : 2-O-iso*propylidene*-D-*glucose* 6-*nitrate*. Fuming nitric acid (0·27 ml.) in acetic anhydride (2 ml.) was added to 3 : 5-*O*-benzylidene-1 : 2-*O*-*iso*propylidene-D-glucose [21] (1·27 g.) suspended in acetic anhydride (5 ml.) at 0°, and the mixture was left at room temperature for 10 min. The product, precipitated when the mixture was poured into ice-water, recrystallised from methanol as 3 : 5-O-*benzylidene*-1 : 2-O-iso*propylidene*-D-*glucose* 6-*nitrate* (0·95 g., 66%), m. p. 86°, $[\alpha]_D^{22}$ +12·1° (*c* 0·6) (Found: C, 54·7; H, 5·5. $C_{16}H_{19}O_8N$ requires C, 54·4; H, 5·4%).

A solution of 3 : 5-*O*-benzylidene-6-deoxy-6-iodo-1 : 2-*O*-*iso*propylidene-D-glucose [22] (0·1 g.) and silver nitrate (0·06 g.) in methyl cyanide (5 ml.) was boiled under reflux for 8 hr. The cooled mixture was filtered and evaporated to a syrup which, recrystallised twice from methanol, gave the 6-nitrate (0·075 g., 85%), m. p. 85—86°.

(e) 2 : 3-5 : 6-*Di*-O-iso*propylidene*-D-*mannose* 1-*nitrate*. The solution obtained by adding fuming nitric acid (1·4 ml.) and acetic anhydride (3·5 ml.) to a suspension of 2 : 3-5 : 6-di-*O*-*iso*propylidene-D-mannose (2·61 g.) in acetic anhydride (7 ml.) at 0°, after 40 min. at room temperature, was poured into ice-water. The resulting solid recrystallised from ether (25 ml.), to yield 2 : 3-5 : 6-*di*-O-iso*propylidene*-D-*mannose* 1-*nitrate* (2·82 g., 90%), m. p. 83·5—84° (Found: C, 46·9; H, 6·3; N, 4·7. $C_{12}H_{19}O_8N$ requires C, 47·2; H, 6·3; N, 4·6%). The product decomposed with the evolution of brown fumes after 15 days in an airtight bottle.

(f) *Methyl* 2 : 3 : 4-*tri*-O-*acetyl*-α-D-*glucoside* 6-*nitrate*. Methyl cyanide (100 ml.) containing methyl 2 : 3 : 4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucoside [23] (3·3 g.) and silver nitrate (1·9 g.) was boiled under reflux for 4 hr. The mixture was then cooled to 0°, filtered, and evaporated to dryness. The residue was extracted thrice with boiling chloroform, and the combined extracts were evaporated to a solid which, recrystallised from aqueous methanol, was methyl 2 : 3 : 4-tri-*O*-acetyl-α-D-glucoside 6-nitrate (2·0 g., 70%), m. p. 112·5—113·5°, $[\alpha]_D^{19}$ +125·8° (*c* 1·2).

(g) *Methyl* 4 : 6-O-*benzylidene*-α-D-*glucoside* 3-*nitrate*. Fuming nitric acid (0·97 ml., 0·022 mole) was added gradually to a solution of methyl 4 : 6-*O*-benzylidene-α-D-glucoside (5·65 g., 0·02 mole) in chloroform (30 ml.) and acetic anhydride (15 ml.) at 0°. After 1 hr. the mixture was neutralised with dilute aqueous potassium carbonate. The chloroform layer was washed twice with water before being evaporated. The resulting syrup was chromatographed in benzene solution. Elution with benzene, followed by evaporation of the solvent, gave an unidentified syrup (0·4 g.). The solid, obtained by elution with chloroform followed by evaporation, recrystallised from chloroform–light petroleum as methyl 4 : 6-*O*-benzylidene-α-D-glucoside 3-nitrate [4] (1·8 g., 28%), $[\alpha]_D^{20}$ +112·9° (*c* 1·1), m. p. 171—172°.

(h) *Methyl* 2-O-*methyl*-α-D-*glucoside* 3-*nitrate*. A suspension of Amberlite IR-120(H) (2·2 g.) was stirred in boiling 80% methanol (50 ml.) containing methyl 4 : 6-*O*-benzylidene-2-*O*-methyl-α-D-glucoside 3-nitrate (1·5 g.) for 4·5 hr. The resin was filtered off and washed with methanol;

[19] Gluzman and Klyushnik, *J. Gen. Chem.* (*U.S.S.R.*), 1955, **25**, 2073.
[20] Raymond and Schroeder, *J. Amer. Chem. Soc.*, 1948, **70**, 2785.
[21] Brigl and Gruner, *Ber.*, 1932, **65**, 1428.
[22] Foster, Overend, Stacey, and Wiggins, *J.*, 1949, 2542.
[23] Compton, *J. Amer. Chem. Soc.*, 1938, **60**, 395.

evaporation of the combined washings and filtrate gave a colourless syrup which was chromatographed in benzene. Elution with benzene and with chloroform, followed by evaporation, yielded traces of unidentified syrup. The column was then washed with ethanol; removal of the solvent gave colourless syrup (0·7 g.) which crystallised to give *methyl* 2-O-*methyl*-α-D-*glucoside* 3-*nitrate*, m. p. 89—90° (Found: C, 38·2; H, 6·0. $C_8H_{15}O_8N$ requires C, 38·0; H, 6·0%).

The product (0·3 g.), powdered anhydrous zinc chloride (0·3 g.), and benzaldehyde (2 ml.) were shaken at room temperature for 24 hr. When the mixture was poured into ice-water, two layers formed. The upper layer was decanted and the other extracted twice with chloroform. The combined extracts were dried, and excess of benzaldehyde and solvent were removed by distillation under reduced pressure. The resultant syrup, recrystallised twice from light petroleum, was methyl 4 : 6-*O*-benzylidene-2-*O*-methyl-α-D-glucoside 3-nitrate (0·31 g., 75%), m. p. 116°.

(i) 1 : 2-O-cyclo*Hexylidene*-D-*glucose* 3-*nitrate*. Amberlite IR-120(H) (14 g.) and 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-nitrate (10 g.) were boiled for 4·5 hr. under reflux in stirred methanol (120 ml.) containing water (30 ml.). After being filtered, the solution was evaporated to a syrup, which was extracted with hot chloroform. Evaporation of the extract yielded a syrup which was shaken with petroleum, then crystallised from carbon tetrachloride and water successively, to give needles of 1 : 2-O-cyclo*hexylidene*-D-*glucose* 3-*nitrate* (5·0 g., 63%), m. p. 95°, $[\alpha]_D^{18}$ −1·0° (*c* 1·0) (Found: C, 47·3; H, 6·3; N, 4·5. $C_{12}H_{19}O_8N$ requires C, 47·2; H, 6·3; N, 4·6%).

Oxidation of the 3-nitrate with aqueous periodic acid, followed by steam-distillation of the solution, gave formaldehyde, identified as the dimedone derivative, m. p. 188°.

*cyclo*Hexanone (3 ml.) containing concentrated sulphuric acid (0·145 ml.) and 1 : 2-*O*-*cyclo*hexylidene-D-glucose 3-nitrate (1·0 g.) was shaken for 5 hr. at room temperature. *n*-Heptane was added to the mixture, which was warmed until two layers were formed. The heptane layer was decanted, shaken with potassium carbonate solution, washed with water, dried ($Na_2SO_4$), and evaporated. The syrup, crystallised from warm methanol, gave 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-nitrate (0·86 g., 68%), m. p. 81—82°.

*Preparation of Methyl* β-L-*Arabinoside* 2 : 3 : 4-*Tritoluene*-p-*sulphonate*.—Solutions of methyl β-L-arabinoside (10 g.) in pyridine (30 ml.) and toluene-*p*-sulphonyl chloride (54 g.) in pyridine (100 ml.) were mixed at 0°, and the resulting solution was left at room temperature for 8 days. The product, isolated by being precipitated in ice-water and crystallised from ethanol, was *methyl* β-L-*arabinoside* 2 : 3 : 4-*tritoluene*-p-*sulphonate* (28 g., 74%), m. p. 113—114°, $[\alpha]_D^{20}$ +95·6° (*c* 0·7) (Found: C, 51·8; H, 4·9. $C_{27}H_{30}O_{11}S_3$ requires C, 51·5; H, 4·8%).

*Reactions of Nitrates and Sulphonates with Sodium Methoxide in Methanol*.—(a) 1 : 2-5 : 6-*Di*-O-cyclo*hexylidene*-D-*glucose* 3-*nitrate*. (i) The 3-nitrate (3·85 g., 0·01 mole) in methanolic sodium methoxide (50 ml.; sodium, 0·26 g., 0·011 mole) was boiled under reflux for 8 hr. The coloured mixture was evaporated and the residue extracted with water. The precipitate was ground, extracted again with water, collected, and dried in a desiccator. This solid (3·42 g.), m. p. 107—109°, recrystallised twice from *n*-heptane, was 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose (2·0 g., 59%), $[\alpha]_D^{24}$ +1·85° (*c* 1·7), m. p. 131·5—132·5°. Starting compound (0·74 g., 19%) was isolated from the mother-liquor.

(ii) A solution of the nitrate (7·697 g., 1 mole) in anhydrous methanol (100 ml.) containing sodium (0·7074 g., 1·5 mole) was boiled under reflux for 13 hr. The evaporated mixture, after extraction with chloroform, was dissolved in water. An aqueous extract of the chloroform solutions was combined with this solution and the volume was made up to 250 ml. Titration of aliquot parts against hydrochloric acid showed that 1·49 equivalents of sodium had been consumed during the reaction. 10% Aqueous potassium iodide (5 ml.) was added to each neutralised aliquot part, and carbon dioxide was bubbled through the whole. 2N-Hydrochloric acid (10 ml.) was introduced below the liquid surface; the liberated iodine, titrated with sodium thiosulphate, was equivalent to 34% of nitrite ion. When a portion of the original solution was first boiled with ammonium chloride (0·5 g.) for 10 min. to decompose nitrite, no iodine was liberated on addition of potassium iodide and hydrochloric acid, showing the absence of oxidising agents other than sodium nitrite.

The chloroform extracts of the original reaction mixture were evaporated to a syrup which, crystallised from light petroleum (b. p. 80—100°), was 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose (4·463 g., 69% of nitrate consumed), m. p. 132°. The concentrated mother-liquor crystallised from methanol, to give starting compound (0·365 g.).

XUM

(iii) A solution of the nitrate (3·863 g.) was treated with sodium (0·355 g.) in methanol (50 ml.) as in the preceding experiment. The dark brown mixture was filtered through sintered glass, and its volume was made up to 100 ml. with anhydrous methanol. This solution did not decolorise bromine in carbon tetrachloride or permanganate in aqueous acetone. A portion (50 ml.) of the solution was evaporated and the residue was extracted several times with water. The volume of the extract was made up to 100 ml. After it had been neutralised with 2N-sulphuric acid, mixed with ammonium sulphamate (0·4 g.) and 2N-sulphuric acid (6 ml.), and kept overnight, the solution was halved and raised nearly to the b. p. Then to each half was added nitron (0·5 g.) in 5% acetic acid (5 ml.). The solutions were cooled in ice-water for 2 hr., and the precipitates of nitron nitrate were collected, washed, and dried to constant weight (0·3902 g., 0·3893 g., equiv. to 42% of nitrate ion).

(b) 1 : 2-5 : 6-*Di*-O-cyclo*hexylidene*-D-*glucose* 3-*toluene*-p-*sulphonate*. (i) Methanol (50 ml.) containing sodium (0·6 g.) and the 3-toluene-*p*-sulphonate (5·6 g.) was boiled under reflux for 23 hr. Acetic acid (0·3 ml.) was added, and methanol was evaporated. The solid residue was shaken with warm benzene; evaporation of the benzene extract yielded a white solid, which, recrystallised from *n*-heptane, was 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose (3·7 g., 94%).

(ii) When the quantity of sodium used was 0·02 g., unchanged starting compound (96%) was recovered.

(iii) When the toluene-*p*-sulphonate was treated as in (i) but at room temperature for 21 days, starting compound (91%) was recovered.

(c) 1 : 2-3 : 4-*Di*-O-iso*propylidene*-D-*galactose* 6-*toluene*-p-*sulphonate*. A solution of sodium (0·33 g.) and the 6-toluene-*p*-sulphonate (2·0 g.) in methanol (25 ml.) was boiled under reflux for 25 hr. Acetic acid (0·1 ml.) was added, and the evaporated mixture was extracted twice with chloroform. Evaporation of the combined extracts gave a colourless oil which did not decolorise bromine in carbon tetrachloride or potassium permanganate in aqueous acetone. The oil, chromatographed in benzene solution, yielded, on elution with benzene, starting compound (0·1 g., 5%) and, on elution with chloroform, 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose (1·12 g., 90%), identified by conversion into the corresponding 6-nitrate.

When a similar reaction was stopped after 2 hr. starting compound (84%) was recovered.

(d) 1 : 2-3 : 4-*Di*-O-iso*propylidene*-D-*galactose* 6-*nitrate*. A solution of this nitrate (3·06 g., 1 mol.) in methanol (50 ml.) containing sodium (0·69 g.) was boiled under reflux for 5 hr. Excess of sodium methoxide was neutralised with acetic acid, the solvent was evaporated, and the residue was extracted with chloroform. Evaporation of the extract gave a syrup which did not decolorise bromine or permanganate. Chromatography, as described in the preceding experiment, gave unchanged compound (1·15 g., 37%) and 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose (0·97 g., 37%), identified as its toluene-*p*-sulphonate.

The reaction mixture, boiled under reflux for 1 hr. only, yielded the same products (54 and 25% respectively).

*Reaction of Nitrates and Sulphonates with Sodium Iodide.*—In these experiments each reaction mixture was evaporated to dryness; the residue was extracted twice with chloroform, and the chloroform solution was washed successively with sodium thiosulphate solution and water. The chloroform was evaporated and the resulting product was crystallised.

(a) 1 : 2-5 : 6-*Di*-O-cyclo*hexylidene*-D-*glucose* 3-*nitrate*. Acetone (20 ml.) containing sodium iodide (4·2 g.) and 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-nitrate (3·5 g.) was heated in a sealed tube at 100° for 48 hr. The product, recrystallised from *n*-heptane, was 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose (1·83 g., 59%), m. p. 129—130°. Unchanged 3-nitrate (0·21 g., 6%) was isolated from the mother-liquor.

(b) 1 : 2-3 : 4-*Di*-O-iso*propylidene*-D-*galactose* 6-*nitrate*. *iso*Butyl methyl ketone (50 ml.) containing sodium iodide (1·8 g.) and 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose 6-nitrate (3·06 g.) was boiled under reflux for 47 hr. The syrup, crystallised from aqueous ethanol, was 6-deoxy-6-iodo-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose (2·04 g., 55%), m. p. 71°, $[\alpha]_D^{21}$ −52·5° (*c* 1·0).

A sealed tube containing the 6-nitrate (1·50 g.), sodium iodide (0·9 g.), and acetone (20 ml.) was heated at 100° for 47 hr. The product was 6-deoxy-6-iodo-1 : 2-3 : 4-di-*O*-*iso*propylidene-galactose (1·01 g., 55%), m. p. 71°.

(c) Treatment of methyl β-L-arabinoside 2 : 3 : 4-tritoluene-*p*-sulphonate and 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-toluene-*p*-sulphonate with sodium iodide in acetone at 100° for 45 hr. gave unchanged compounds in yields of 73% and 78% respectively.

(d) When methyl **4**:6-*O*-benzylidene-3-deoxy-3-iodo-α-D-glucoside [24] (0·2 g.) was heated with sodium iodide (0·4 g.) in anhydrous acetone (5 ml.) at 100° for 4 days in a sealed tube, very little discolouring occurred. Evaporation of the solvent followed by recrystallisation from methanol yielded unchanged starting compound (75%), m. p. 193°, $[\alpha]_D^{20}$ −9·3° (*c* 0·5).

*Reduction of* **1**:2-3:4-*Di*-O-iso*propylidene*-D-*galactose* **6**-*Nitrate with Lithium Aluminium Hydride.*—A solution of the 6-nitrate (3·06 g.) in anhydrous ether (30 ml.) was added dropwise during 1 hr. to a stirred suspension of lithium aluminium hydride (0·6 g.) in boiling anhydrous ether (40 ml.). After another 48 hours' boiling, water (40 ml.) was added cautiously to the mixture. The aqueous layer was separated and extracted with more ether (50 ml.). The combined ethereal solutions, washed with dilute sulphuric acid and with water, were dried ($K_2CO_3$–$Na_2SO_4$). Evaporation of the solvent yielded a syrup which was chromatographed in benzene. Elution with benzene, followed by crystallisation of the solid from aqueous ethanol, gave unchanged starting compound (0·24 g., 8%), m. p. 61°. Elution with chloroform yielded a colourless syrup (1·54 g.) which, distilled at 0·1 mm., was **1**:2-3:4-di-*O*-*iso*propylidene-D-galactose (57%). This was identified as the 6-nitrate (1·43 g., 83%), m. p. 61°.

A similar reaction, stopped after 17 hr., gave unchanged compound (39%) and **1**:2-3:4-di-*O*-*iso*propylidene-D-galactose (33%).

*Reaction of Nitrates, Sulphonates, and Acetates with Sodium Nitrite.*—(a) *Methyl* **4**:6-O-*benzylidene*-α-D-*glucoside* **3**-*nitrate.* A solution of the 3-nitrate (4·62 g.) and sodium nitrite (2·92 g.) in 80% ethanol (50 ml.) was boiled under reflux for 7 days. On cooling, the solution deposited crystals which were collected, dried, and recrystallised from alcohol, to give starting compound (52%), m. p. 168—169°. Evaporation of the reaction mother-liquor gave a syrup which crystallised from benzene, to yield methyl **4**:6-*O*-benzylidene-α-D-glucoside (0·53 g., 15%), m. p. 160°.

(b) *Methyl* **4**:6-O-*benzylidene*-α-D-*glucoside* **2**:**3**-*dinitrate.* The dinitrate (3 g.) and sodium nitrite (1·86 g.) were boiled under reflux (moisture excluded) in ethanol (50 ml.) for 21 hr. The evaporated mixture was dissolved in benzene, filtered, and chromatographed. Elution with benzene, followed by chloroform, yielded fractions which were recrystallised, to give starting compound (0·95 g., 32%), m. p. 122·5—123°, and methyl **4**:6-*O*-benzylidene-α-D-glucoside 3-nitrate (0·89 g., 34%), m. p. 169—170°.

When methyl **4**:6-*O*-benzylidene-α-D-glucoside **2**:3-dinitrate (2 g.) was boiled under reflux in 80% ethanol alone for 4 days, starting compound (75%) only was recovered.

(c) *Methyl* **4**:6-O-*benzylidene*-α-D-*glucoside* **2**-*methanesulphonate* **3**-*nitrate.* A solution of this ester (3·2 g.) and sodium nitrite (1·66 g.) in 80% ethanol (40 ml.) was boiled under reflux for 21 hr. The products, isolated by chromatography as in the preceding experiment, were starting compound (1·3 g., 41%), m. p. 129—130°, and methyl **4**:6-*O*-benzylidene-α-D-glucoside 2-methanesulphonate (1·2 g., 42%), m. p. 132°.

(d) *Methyl* **4**:6-O-*benzylidene*-2-O-*methyl*-α-D-*glucoside* **3**-*nitrate.* This compound (2·5 g.) was boiled with sodium nitrite (1·54 g.) as described in the previous experiment. Starting compound (2·2 g., 88%) was recovered.

(e) **1**:2-5:6-*Di*-O-cyclo*hexylidene*-D-*glucose* **3**-*nitrate.* A solution of this nitrate (3·85 g.) and sodium nitrite (2·07 g.) in 80% ethanol (50 ml.) was boiled under reflux for 3 days. The evaporated mixture was extracted twice with chloroform. Evaporation of the combined extracts yielded a syrup which, dissolved in the minimum amount of hot methanol and refrigerated, gave starting compound (1·84 g., 48%), m. p. 82°. The concentrated mother-liquor was dissolved in warm *n*-heptane, and the white solid (1·04 g.) which was precipitated on cooling was **1**:2-5:6-di-*O*-*cyclo*hexylidene-D-glucose (31%), m. p. 129—130°.

(f) *Methyl* **2**:**3**:**4**-*tri*-O-*acetyl*-α-D-*glucoside* **6**-*nitrate.* A solution of this nitrate (1 g.) and sodium nitrite (0·29 g.) in 80% ethanol (38 ml.) was boiled under reflux for 2 hr. When cooled, the solution yielded unchanged starting compound (0·83 g., 83%), m. p. 113·5—114·5°. This was redissolved in the mother-liquor, which was then boiled for 16 hr. When the solution was cooled starting compound (0·4 g.) separated. The mother-liquor was then evaporated to dryness and extracted twice with chloroform. Evaporation of the extracts yielded a white solid (0·35 g.) which, after recrystallisation from methanol, was starting compound (0·22 g., total yield 62%), m. p. 113—114°.

(g) **3**:5-O-*Benzylidene*-**1**:2-O-iso*propylidene*-D-*glucose* **6**-*nitrate.* Sodium nitrite (0·29 g.) and **3**:5-*O*-benzylidene-**1**:2-*O*-*iso*propylidene-D-glucose 6-nitrate (0·5 g.) were boiled under

[24] Newth, Richards, and Wiggins, *J.*, 1950, 2356.

reflux in 80% ethanol for 14 hr. The crystals which separated on cooling were collected, dried, and shown to be starting compound (0·26 g., 52%), m. p. 85°. The mother-liquor was evaporated to a syrup which was dissolved in warm benzene (2 ml.). Petroleum (2 ml.) was added, and after cooling, the white solid which was precipitated was collected, dried, and shown to be 3 : 5-*O*-benzylidene-1 : 2-*O*-*iso*propylidene-D-glucose (0·15 g., 34%), m. p. 142°.

(h) 1 : 2-3 : 4-*Di*-O-iso*propylidene*-D-*galactose* 6-*nitrate*. Sodium nitrite (3·39 g.) and 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose 6-nitrate (5·0 g.) were boiled under reflux in 80% ethanol (50 ml.) for 7 days. The mixture was evaporated, and the residue extracted with chloroform. Evaporation of the chloroform extract yielded a syrup, which was chromatographed in benzene (20 ml.). Elution with benzene yielded a solid which, recrystallised from aqueous ethanol, was starting compound (3·9 g., 78%), m. p. 61°. Elution with chloroform (500 ml.) yielded a clear syrup (0·17 g., 4%), shown to be 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose by conversion into its 6-nitrate in high yield.

(i) *Methyl* 4 : 6-O-*benzylidene*-α-D-*glucoside* 2 : 3-*diacetate*. (α) This compound (1·43 g.) and sodium nitrite (0·8 g.) were boiled under reflux in 80% ethanol (25 ml.) for 21 hr. On cooling of the alkaline mixture, starting compound (0·86 g., 60%), m. p. 106°, crystallised. Concentration of the mother-liquor left a residue which was extracted with chloroform. Evaporation of the chloroform yielded a white solid which, recrystallised from water, was methyl 4 : 6-*O*-benzylidene-α-D-glucoside (0·14 g., 5%), m. p. 159°.

(β) The above experiment was repeated, but boiling was continued for 7 days. The alkaline reaction mixture, which smelled of benzaldehyde, was evaporated, and the residue was extracted with chloroform. Concentration of the solution yielded a solid which, recrystallised from hot water, gave methyl 4 : 6-*O*-benzylidene-α-D-glucoside (4·35 g., 79%), m. p. 162—162·5°.

(γ) When the diacetate (2·33 g.) was boiled in solvent (50 ml.) alone for 6 days, starting compound (1·45 g., 62%) only was obtained.

(j) *Toluene*-p-*sulphonates and methanesulphonates*. Methyl 4 : 6-*O*-benzylidene-α-D-glucoside 2 : 3-dimethanesulphonate (4·62 g.) was boiled under reflux in ethanol (80 ml.) containing chloroform (35 ml.), water (10 ml.), and sodium nitrite (2 g.) for 21 hr. Starting compound (4·4 g., 95%), m. p. 185°, was recovered.

The corresponding 2 : 3-ditoluene-*p*-sulphonate (5·9 g.) was boiled for 5 days with the mixture described in the previous experiment. Unchanged starting compound (5·2 g., 88%), m. p. 146°, $[\alpha]_D^{17}$ +12·2° (*c* 1·6), was recovered.

A solution of 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose 6-toluene-*p*-sulphonate (1·0 g.) and sodium nitrite (0·86 g.) in 80% ethanol (10 ml.) was boiled under reflux for 48 hr. Starting compound (91%) was recovered.

*Action of Sodium Acetate and of Sodium Nitrate in* 80% *Ethanol on Methyl* 4 : 6-O-*Benzylidene*-α-D-*glucoside* 2 : 3-*Dinitrate*.—The dinitrate (6·0 g.) in 80% ethanol (120 ml.) containing sodium acetate (6·6 g.) was boiled under reflux for 7 days. Evaporation of the solvent yielded a white solid which was shaken with chloroform (100 ml.) and water (100 ml.). The aqueous layer was extracted with chloroform, the combined chloroform extracts were evaporated, and the residue was chromatographed in benzene. Elution with benzene (400 ml.) and chloroform (400 ml.) in turn yielded starting compound (2·5 g., 42%), m. p. 122°, and methyl 4 : 6-*O*-benzylidene-α-D-glucoside 3-nitrate (1·4 g., 37%), m. p. 171—172°.

In a similar experiment, the dinitrate (3·72 g.) and sodium nitrate (2·55 g.) in 80% ethanol (60 ml.) were boiled under reflux for 20 hr. Water (20 ml.) was added, and, on cooling, starting compound (3·60 g., 97%), m. p. 122—123°, was obtained.

*Action of Sodium Acetate in* 80% *Ethanol on* 1 : 2-5 : 6-*Di*-O-cyclo*hexylidene*-D-*glucose* 3-*Nitrate*.—Sodium acetate (4·08 g.) and 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose 3-nitrate (3·85 g.) were boiled in 80% ethanol (48 ml.) for 5 days. The residue obtained by evaporating the solution was shaken with chloroform (50 ml.) and water (50 ml.), and the aqueous layer was shaken with further chloroform (50 ml.). The combined chloroform extracts were evaporated, and the residue was dissolved in hot methanol. On cooling, starting compound (3·33 g., 87%), m. p. 82·5—83°, separated. The mother-liquor was evaporated, and the residue was dissolved in a small quantity of warm *n*-heptane. This solution, on cooling, yielded 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-D-glucose (0·1 g., 3%), m. p. 131°.

*Preparation of Methyl* 4-O-*Methyl*-β-D-*glucoside*.—A solution of methyl β-D-glucoside 2 : 3 : 4 : 6-tetranitrate [1] (3·74 g., 0·01 mole) and sodium nitrite (3·45 g., 0·05 mole) in 80% ethanol (20 ml.) was boiled under reflux for 5·5 hr. The evaporated mixture was dried in a

vacuum-desiccator, then extracted twice with boiling chloroform. Evaporation of the combined extracts gave a syrup which was chromatographed in benzene. Elution with benzene yielded a trace of syrup, which was discarded. Further elution with chloroform gave a colourless syrup (1·6 g., 49%) which was substantially methyl β-D-glucoside 2 : 3 : 6-trinitrate, $[\alpha]_D^{15}$ −10·8° (*c* 1·1). Finally, washing the column with ethanol gave unidentified syrup (0·38 g.).

Silver oxide (6 g.) was added in portions (0·5 g.) during 5 hr. to a boiling solution of the trinitrate (1·24 g.) in methyl iodide (25 ml.). After a further 19 hours' boiling the solution was filtered and evaporated to a syrup which was chromatographed in benzene. Evaporation of the benzene eluent left a syrup, a portion (0·3 g.) of which was dissolved in glacial acetic acid (2 ml.). Zinc dust and iron filings were added gradually to the solution, and the mixture was warmed gently until no more gas was evolved. Water (20 ml.) was added and the acid was neutralised with sodium carbonate. The solution was filtered and evaporated and the residue was dried in a desiccator. This solid was extracted thrice with boiling ethyl acetate (20 ml.), and the combined extracts were evaporated to 2 ml. On cooling, crystals of methyl 4-*O*-methyl-β-D-glucoside (0·12 g., 60%) were formed, which after recrystallisation twice from ethyl acetate, had m. p. 101—102°. Haywärd and Purves [18] record m. p. 101°.

*Methyl* β-D-*Glucoside* 4-*Acetate* 2 : 3 : 6-*Trinitrate*.—Ice-cold acetic anhydride (2 ml.) was added to a solution of methyl β-D-glucoside 2 : 3 : 6-trinitrate (0·4 g.) in pyridine (2 ml.), and the solution was left at room temperature for 6 days. The solid product, which separated when the solution was poured into ice-water, after recrystallisation from ethanol–light petroleum, was *methyl* β-D-*glucoside* 4-*acetate* 2 : 3 : 6-*trinitrate*, m. p. 91° (Found: C, 29·8; H, 3·6. $C_9H_{13}O_{13}N_3$ requires C, 29·4; H, 3·5%).

The authors are indebted to Courtaulds Scientific and Educational Trust Fund for a Postgraduate Research Scholarship (to T. C. S.).

UNIVERSITY OF LONDON, KING'S COLLEGE,
STRAND, LONDON, W.C.2.
[Present address (J. H.):
BRITISH COTTON INDUSTRY RESEARCH ASSOCIATION,
SHIRLEY INSTITUTE, DIDSBURY, MANCHESTER, 20.] [*Received, August 9th*, 1957.]

---

## 104. *Nucleotides. Part XLIII.* The Use of Cyanamide Derivatives in Pyrophosphate Synthesis. Syntheses of* P¹-*Adenosine-5′* P²-*Uridine-5′ Pyrophosphate and of Cytidine-5′ Pyrophosphate.*

By G. W. KENNER, C. B. REESE, and SIR ALEXANDER TODD.

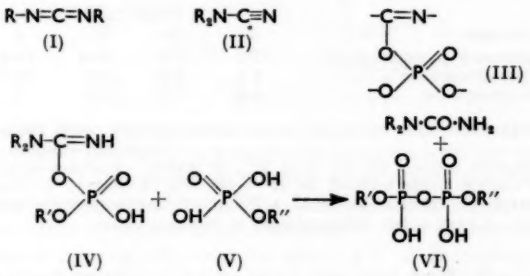
Condensations of phosphates to pyrophosphates can be effected in aqueous solutions by means of dimethylcyanamide or cyanamide. $P^1$-Adenosine-5′ $P^2$-uridine-5′ pyrophosphate has been synthesised by these methods and by the established phosphorochloridate and carbodi-imide procedures; the symmetrical $P^1P^2$-dialkyl pyrophosphates were invariably obtained as by-products. Cytidine-5′ pyrophosphate is obtained in satisfactory yield from cytidine-5′ phosphate by using dimethylcyanamide.

THE synthesis of nucleotide coenzymes has been the object of much research in these laboratories during the past decade. Since all coenzymes of this group so far identified are either monoesters of pyro- or poly-phosphoric acids or unsymmetrical diesters of pyrophosphoric acid in which at least one esterifying group is a nucleoside derivative, the discovery and evaluation of new methods for synthesising unsymmetrical pyrophosphates has been a continuing feature of our researches. The preparation of pyrophosphates from phosphates by means of carbodi-imides [1] (I) is now a well-established procedure in the nucleotide field.[2,3] Further, several schemes of synthesis involving imidoyl phosphates

* Part XLII, *J.*, 1957, 3297.

[1] Khorana and Todd, *J.*, 1953, 2257.
[2] *E.g.*, Khorana, *J. Amer. Chem. Soc.*, 1954, **76**, 3517; Kenner, Todd, and Webb, *J.*, 1954, 2843.
[3] Kennedy, *J. Biol. Chem.*, 1956, **222**, 185; Hughes, Kenner, and Todd, *J.*, 1957, 3733.

(III) have been devised,[4] which bear some resemblance to the carbodi-imide method since the latter probably proceeds by way of an intermediate adduct of a phosphoric acid and the carbodi-imide. It seemed likely that dialkylcyanamides (II), which are isomeric with the corresponding dialkylcarbodi-imides (I) might generate with mono- or di-esters of phosphoric acids highly reactive adducts, such as (IV), of a type similar to that postulated for the




carbodi-imide reaction.[1] If so, dialkylcyanamides should be capable of forming pyrophosphates from mono- and di-esters of phosphoric acid. That this is the case was confirmed by the experiments described below.

In preliminary experiments it was shown that $P^1P^2$-dibenzyl pyrophosphate (VI; R′ = R″ = Ph·$CH_2$) is formed in *ca.* 50% yield when benzyl dihydrogen phosphate (2 mols.) is refluxed with dimethylcyanamide (1 mol.) in methyl cyanide. Dimethylcyanamide is readily available and has good solvent properties; when diluted with about 10% of water it gives a mixture which dissolves a number of nucleotides. In extending our experiments to the nucleotide field we therefore dispensed with added solvent and simply condensed adenosine-5′ phosphate with uridine-5′ phosphate by heating them in aqueous dimethylcyanamide. This condensation was selected as being analogous to coenzyme synthesis although the product (VI; R′ = adenosine-5′; R″ = uridine-5′), which had not previously been prepared, is not known to occur naturally or expected to have any unusual biological action. In a preparative experiment the reaction mixture contained 30% of water and was buffered with a little pyridine. The solution was heated for 13 hours at 92° and the products (see Table) were isolated by anion-exchange chromatography. The yield of each product was reckoned from the weights of lithium salt actually isolated by rather wasteful precipitations and therefore do not give a true estimate of the total amount of pyrophosphates formed. Paper chromatography showed that the total yield of pyrophosphates was *ca.* 50% under these conditions and that higher yields could be obtained by raising the temperature or reducing the amount of water in the medium. At temperatures below 80° reaction was too slow for preparative purposes. Condensation still occurred when 50% of water was present and even then hydrolysis of the dimethylcyanamide to *NN′*-dimethylurea was negligible when the reaction was carried out at 100°; in marked contrast massive quantities of *NN′*-di*cyclo*hexylurea are produced from di*cyclo*hexylcarbodi-imide when it is used in a similar fashion in large excess in presence of water.[2] Thus the dimethylcyanamide method, which has the merit of being easy to handle, may well be of considerable value for the preparation of fairly stable pyrophosphates.

Our success with dimethylcyanamide encouraged us to examine cyanamide itself as a reagent for pyrophosphate synthesis. Although commonly believed to have structure (II; R = H) it was not excluded that it might react in the carbodi-imide form (I; R = H).[5] The results obtained were, in fact, little different from those obtained with dimethylcyanamide, suggesting that it reacted as (II; R = H). Dimerisation of the cyanamide

[4] Atherton, Morrison, Cremlyn, Kenner, Todd, and Webb, *Chem. and Ind.*, 1955, 1183; Kenner, Todd, and Webb, *J.*, 1956, 1231; Chase, Kenner, Todd, and Webb, *J.*, 1956, 1371.
[5] Cf. Kahovec and Kohlrausch, *Z. phys. Chem.*, 1937, **37**, *B*, 421.

was a serious side reaction, however, and even when the reaction temperature was not allowed to exceed 75° isolation of the products was hampered by the presence of substantial amounts of dimer. For preparative purposes, therefore, dimethylcyanamide is superior.

*Condensations of adenosine-5′ phosphate and uridine-5′ phosphate.*

| Product | Yield (%) * from experiment a | b | c | d | e | f |
|---|---|---|---|---|---|---|
| $P^1$-Adenosine-5′ $P^2$-uridine-5′ pyrophosphate ... | 17·1 | 13·8 | 25·6 | 14·6 | 10·6 | 17·0 |
| $P^1P^2$-Diadenosine-5′ pyrophosphate ..... | 4·4 | 6·8 | 11·1 | 10·1 | 3·6 | 9·1 |
| $P^1P^2$-Diuridine-5′ pyrophosphate ..... | 4·9 | 6·8 | 13·0 | † | 4·4 | 9·8 |

* Moles of dilithium salt, after anion-exchange chromatography, from 100 moles of each starting material. † None was detected.

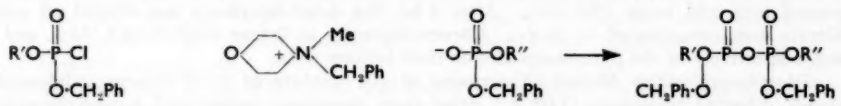
a Dimethylcyanamide method (at 92° with 30% of water). b Cyanamide method (at 75° with 30% of water). c Carbodi-imide method (at 20° with 10% of water). d From 2′ : 3′-*O-iso*propylideneuridine-5′ benzyl phosphorochloridate. e From 2′ : 3′-*O-iso*propylideneadenosine-5′ benzyl phosphorochloridate. f Like e, but debenzylation in methyl cyanide.

A comparative experiment was also made using di*cyclo*hexylcarbodi-imide with the same nucleotides. The variation in total yield between the three experiments (a, b, c in Table) is not very significant since optimum conditions were not observed, but the proportions of the three products deserve comment. It can readily be deduced that, in these reactions, if intermediates such as (IV) are produced equally readily from both the phosphates used as starting materials and if they react further equally rapidly with either starting material, then the yield of unsymmetrical pyrophosphate should be twice as great as that of each of the symmetrical esters. The experiments with cyanamide (b) and di*cyclo*hexylcarbodi-imide (c) conform to this pattern and too much weight should not be given to the slightly increased proportion of unsymmetrical product obtained by using dimethylcyanamide (a). Apparently the structures of adenosine-5′ phosphate and uridine-5′ phosphate are so similar that the above conditions are effectively fulfilled, and indeed this was not unexpected. On the other hand certain carbodi-imide condensations in which one of the reactants was a dipolar ion and the other a simple nucleotide have given results which deviate greatly from this pattern; in such cases one of the symmetrical pyrophosphates was formed in only negligible amount.[3]

Although the elementary analysis of the $P^1$-adenosine-5′ $P^2$-uridine-5′ pyrophosphate obtained from its dilithium salt, and its acidic hydrolysis to uridine-5′ phosphate and adenine, left little room for doubt as to its structure, an alternative synthesis by the phosphorochloridate route was undertaken. The 4-methyl-4-benzylmorpholinium salt (VIII; R″ = 2′ : 3′-*O-iso*propylideneadenosine-5′) of 2′ : 3′-*O-iso*propylideneadenosine-5′ benzyl phosphate was prepared from the dibenzyl ester and 4-methylmorpholine [6] and then brought into reaction with 2′ : 3′-*O-iso*propylideneuridine-5′ benzyl phosphorochloridate [7] (VII; R′ = 2′ : 3′-*O-iso*propylideneuridine-5′). The resulting gum, which was presumed to be mainly the fully esterified pyrophosphate (IX; R′ = 2′ : 3′-*O-iso*propylideneuridine-5′, R″ = 2′ : 3′-*O-iso*propylideneadenosine-5′), was treated with ammonium thiocyanate in ethyl methyl ketone solution and then with dilute acid in order to remove the benzyl [8] and *iso*propylidene residues. Anion-exchange chromatography of the product showed it to be a mixture of the desired material and $P^1P^2$-diadenosine-5′ pyrophosphate (see Table, expt. d). After this disconcerting outcome, the synthesis was carried out with the reverse orientation of groups (*viz.*, R′ = 2′ : 3′-*O-iso*propylideneadenosine-5′, R″ = 2′ : 3′-*O-iso*propylideneuridine-5′). In this case the results (Table, expt. e) were similar to those of " random " condensations with cyanamides or di*cyclo*hexylcarbodi-imide. The yield was improved, without altering greatly the proportions

[6] Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 875.
[7] Kenner, Todd, and Weymouth, *J.*, 1952, 3675.
[8] Atherton and Morrison, B.P. 675,779.

of the products, by substituting methyl cyanide for ethyl methyl ketone as the solvent for debenzylation (Table, expt. f). The origin of these mixtures is not far to seek, and we have suspected for some time that syntheses may take this course.[9] Fully esterified pyrophosphates very easily undergo exchange reactions with anions of phosphates,[10] and



(VII) (VIII) (IX)

consequently the product (IX) as it is formed will compete with the phosphorochloridate (VII) for the salt (VIII). This exchange reaction either regenerates the reagents or leads to one symmetrical pyrophosphate and sets free the anion which may eventually be incorporated in the other symmetrical pyrophosphate. The assumption, for which there is at present no supporting evidence, that the anion of 2′ : 3′-*O*-*iso*propylideneadenosine-5′ benzyl phosphate is considerably more nucleophilic than the corresponding anion in the uridine series would account for the difference between the results of the two experiments (d and e). A pyrophosphate is of course less susceptible to exchange reactions when it is not fully esterified and bears a negative charge. Hence syntheses of the phosphorochloridate type should be more efficient when they avoid the fully esterified pyrophosphate (*e.g.*, IX) by starting from the salt of a monoalkyl instead of a dialkyl phosphate. In line with this, thymidine-5′ pyrophosphate and triphosphate have been obtained in high yields [11] whereas the older type of synthesis led to many by-products. It is of interest in this connection that coenzyme syntheses in which phosphorochloridates [12] were used also involved coupling with salts of phosphoric monoesters.

The utility of dimethylcyanamide as a reagent for preparing nucleoside pyrophosphates has also been tested in the synthesis of cytidine-5′ pyrophosphate. This seemed a particularly suitable case since earlier experiments had shown that the phosphorochloridate route gave very low yields of a very impure product. When cytidine-5′ phosphate was heated in aqueous dimethylcyanamide with 2 mols. of benzyl dihydrogen phosphate and the product debenzylated, cytidine-5′ pyrophosphate was obtained in *ca.* 40% yield.

## Experimental

*Dimethylcyanamide Method* (*Experiment a*).—A solution of adenosine-5′ phosphate (69·4 mg.) and uridine-5′ phosphate (64·8 mg.) in water (2 c.c.), containing 5% of pyridine, and dimethylcyanamide (4 c.c.) was heated at 92° during 13 hr. No precipitate appeared. The residue from evaporation under reduced pressure was dissolved in water (30 c.c.), and passed through a column (3 cm. × 1 cm.$^2$) of Dowex-2 resin (chloride form). The column was thoroughly washed with water, in order to remove any pyridine, and then developed with hydrochloric acid as follows: 0·003N-acid (1 l.) removed all the starting materials; 0·005N-acid (0·7 l.) removed $P^1P^2$-diadenosine-5′ pyrophosphate; 0·01N-acid (0·9 l.) removed $P^1$-adenosine-5′ $P^2$-uridine-5′ pyrophosphate; 0·035N-acid (1·5 l.) removed $P^1P^2$-diuridine-5′ pyrophosphate. The pyrophosphate solutions were separately neutralised with lithium hydroxide, concentrated under reduced pressure to less than 1 c.c., and diluted with acetone–ethanol (85 : 15). The precipitated lithium salts were centrifuged, washed with acetone, and dried; 6·0, 22·7, and 6·3 mg. respectively were obtained.

*Cyanamide Method* (*Experiment b*).—The same quantities of nucleotides as in experiment a were dissolved in water (1·5 c.c.) containing 5% of pyridine. Cyanamide (3 g.) was added and

[9] Curry, Ph.D. Thesis, Cambridge, 1952, p. 86.
[10] Mason and Todd, *J.*, 1951, 2267; Corby, Kenner, and Todd, *J.*, 1952, 1234.
[11] Mrs. B. Griffin, unpublished work.
[12] Christie, Kenner, and Todd, *J.*, 1954, 46; Michelson and Todd, *J.*, 1956, 3459.

the mixture was kept at 75° during 12 hr. before being worked up in the same way as before. The yields of lithium salts were 9·4, 18·4, and 9·3 mg. respectively.

*Carbodi-imide Method* (*Experiment c*).—The same quantities of nucleotides as in experiments a and b were dissolved in water (1 c.c.) and pyridine (10 c.c.). Di*cyclo*hexylcarbodi-imide (2 c.c.) was added and the mixture was shaken at room temperature during 40 hr. It was then poured into cold water (200 c.c.). After 2 hr. the di*cyclo*hexylurea was filtered off and the filtrate was concentrated to 20 c.c. Chromatography as before yielded 16·2, 34·1, and 16·7 mg. respectively of the pyrophosphates as their lithium salts.

*Phosphorochloridate Method* (*Experiment d*).—A mixture of 2′ : 3′-*O*-*iso*propylideneadenosine-5′ dibenzyl phosphate (1·02 g.; dried over phosphoric oxide) and 4-methylmorpholine (8·5 c.c.) was kept at 100° during 1 hr. before being evaporated under reduced pressure. The morpholinium salt was obtained as a resin by repeated dissolution in dry benzene and evaporation. A phosphorochloridate solution was prepared by adding *N*-chlorosuccinimide (0·24 g.) to a solution of 2′ : 3′-*O*-*iso*propylideneuridine-5′ benzyl phosphite (0·789 g.) in benzene (6 c.c.) and methyl cyanide (0·5 c.c.) and keeping the mixture for 2 hr. at room temperature. This phosphorochloridate solution was added rapidly to a stirred solution of the morpholinium salt in dry benzene (20 c.c.) and methyl cyanide (6 c.c.). Stirring was continued for 2 hr., during which a precipitate separated. After its removal the filtrate was evaporated at room temperature to a gum which was mixed with ethyl methyl ketone (30 c.c.) and dry potassium thiocyanate (0·8 g.). The mixture was boiled under reflux on a water-bath during 3 hr. The solid products were collected at a centrifuge, washed with acetone, and dissolved in $\frac{1}{2}$N-hydrochloric acid (21 c.c.). The solution was kept at room temperature for 24 hr. and aqueous barium hydroxide was added until the pH was 5. Barium bromide (0·6 g.) and then ethanol (180 c.c.) were added. The precipitate was collected and dried (0·57 g.); on paper chromatography (see below) it appeared to be almost free from mononucleotides. An aqueous solution of this barium salt was put on to a column (3 cm. × 8 cm.$^2$) of Dowex-2 resin (chloride form), which was washed with 0·01N-hydrochloric acid. The first 200 c.c. removed some adenosine-5′ phosphate, and this was followed in the next 1·8 l. by $P^1P^2$-diadenosine-5′ pyrophosphate, which was isolated as its lithium salt (0·125 g.) as in experiment a. Washing with 0·032N-hydrochloric acid (0·80 l.) removed $P^1$-adenosine-5′ $P^2$-uridine-5′ pyrophosphate (0·175 g. of lithium salt).

*Phosphorochloridate Method* (*Experiment e*).—A solution of 5′-deoxy-5′-iodo-2′ : 3′-*O*-*iso*propylideneuridine (0·724 g.) in dry benzene (16 c.c.) was boiled under reflux with silver dibenzyl phosphate (0·686 g.) during 30 min. The solution was filtered and evaporated to a yellow resin, which was heated with 4-methylmorpholine (8 c.c.) at 100° during 1 hr. The morpholinium salt was obtained as in experiment d and then dissolved in benzene (20 c.c.) and methyl cyanide (14 c.c.). It was then brought into reaction with a phosphorochloridate solution prepared from 2′ : 3′-*O*-*iso*propylideneadenosine-5′ benzyl phosphite (0·847 g.) and *N*-chlorosuccinimide (0·245 g.) in benzene (10 c.c.) and methyl cyanide (1 c.c.). Debenzylation was carried on for 2 hr. in boiling ethyl methyl ketone (30 c.c.) with ammonium thiocyanate (0·8 g.), and the subsequent operations followed the plan of experiment d. When the column was washed with 0·008N-hydrochloric acid, uridine-5′ phosphate appeared in the first 300 c.c. and $P^1P^2$-diadenosine-5′ pyrophosphate in the next 200 c.c., which were added to the 0·01N-acidic washings (1·5 l.); the combined solutions yielded 0·045 g. of lithium salt. $P^1$-Adenosine-5′ $P^2$-uridine-5′ pyrophosphate (0·129 g. of lithium salt) and $P^1P^2$-diuridine-5′ pyrophosphate (0·052 g. of lithium salt) were eluted by 0·03N-acid (1·4 l.) and 0·04N-hydrochloric acid (0·05M in lithium chloride) (1·7 l.) respectively.

*Phosphorochloridate Method* (*Experiment f*).—This experiment was like the foregoing, but with the following modifications. More silver dibenzyl phosphate (0·724 g.) was used and boiling was for 90 min.; the morpholinium salt was dissolved in benzene (10 c.c.) and methyl cyanide (10 c.c.); methyl cyanide (20 c.c.) was substituted for ethyl methyl ketone for the debenzylation. The weight of barium salt was 0·75 g. The $P^1P^2$-diadenosine-5′ pyrophosphate (0·115 g. of lithium salt) was eluted by 0·008N-acid (400 c.c.) and 0·01N-acid (800 c.c.), the $P^1$-adenosine-5′ $P^2$-uridine-5′ pyrophosphate (0·208 g. of lithium salt) by 0·02N-acid (1 l.), and the $P^1P^2$-diuridine-5′ pyrophosphate (0·115 g. of lithium salt) by 0·02N-acid (1·5 l.), 0·05M in lithium chloride.

*Isolation and Identification of* P$^1$-*Adenosine*-5′ P$^2$-*Uridine*-5′ *Pyrophosphate*.—The lithium salt (0·035 g.), obtained from a Dowex-2 column, was dissolved in water (5 c.c.) and added to a column (3 cm. × 0·3 cm.$^2$) of Dowex-50 resin (hydroxonium form), which was washed with

water (25 c.c.). Lyophilisation of the filtrate furnished the *pyrophosphate* as a white powder (Found, in material dried over $P_2O_5$ at room temperature: C, 32·6; H, 4·1; N, 13·8; P, 8·8. $C_{19}H_{25}O_{15}N_7P_2,2{\cdot}5H_2O$ requires C, 32·7; H, 4·3; N, 14·0; P, 8·9%).

The most convenient identification of this pyrophosphate (and its salts) was by paper electrophoresis at pH 4·5 (in a buffer containing 6 g. of sodium acetate and 4·5 c.c. of acetic acid per l.) at 220 v (4·7 v/cm.) for 16 hr. The distance of migration towards the anode was 8·5 cm., while the distances for $P^1P^2$-diadenosine-5′ and $P^1P^2$-diuridine-5′ pyrophosphates were 6·7 cm. and 10·9 cm. respectively.

A sample (*ca.* 1 mg.) of the lithium salt was heated with 0·1N-hydrochloric acid at 100° for 1 hr. Ascending paper chromatography in butan-1-ol–acetic acid–water (5 : 2 : 3 v/v) then separated three components, which were identified by comparison with authentic samples as unchanged pyrophosphate ($R_F$ 0·06), uridine-5′ phosphate ($R_F$ 0·18), and adenine ($R_F$ 0·61). (This system of chromatography was also useful for following the progress of syntheses although it did not separate the unsymmetrical pyrophosphate from the two symmetrical ones.) These identifications were confirmed by paper electrophoresis at pH 4·5.

*Cytidine-5′ Pyrophosphate.*—A solution of cytidine-5′ phosphate (65 mg., 1 mol.) and benzyl dihydrogen phosphate (75 mg., 2 mols.) in aqueous pyridine (1·5 c.c. of a solution containing 5 parts of pyridine and 95 parts of water by volume) and dimethylcyanamide (4 c.c.) was heated at 110—115° for 16 hr. Solvents were removed under reduced pressure, the residue dissolved in 50% aqueous ethanol (10 c.c.), glacial acetic (0·1 c.c.) added, and the solution hydrogenated at atmospheric pressure and room temperature for 3 hr. in presence of palladium oxide (25 mg.) and 10% palladised charcoal (25 mg.). The filtered solution examined by paper chromatography and paper electrophoresis (acetate buffer, pH 4·8) indicated the presence of 3 nucleotide derivatives—cytidine-5′ phosphate, cytidine-5′ pyrophosphate, and another pyrophosphate, presumably $P^1P^2$-dicytidine-5′ pyrophosphate—as well as inorganic phosphate and pyrophosphate. The solution was then put on a Dowex-2 column (chloride form, 3 cm. × 1 cm.$^2$) which was well washed with water and eluted with increasing concentrations of hydrochloric acid. 0·0015N-Hydrochloric acid (1·75 l.) eluted cytidine-5′ phosphate and the presumed $P^1P^2$-dicytidine-5′ pyrophosphate together, with a peak after 900 c.c. Cytidine-5′ pyrophosphate was eluted with 0·003N-hydrochloric acid (1·8 l.) with the peak after 1 l.

The latter eluate was brought to pH 7 with lithium hydroxide and concentrated to *ca.* 3 c.c. A mixture of acetone (85 c.c.) and ethanol (15 c.c.) was added, and the white precipitate of lithium salt centrifuged off, washed with acetone (30 c.c.), and dried. The product was free from inorganic phosphate and ran as a single phosphorus-containing ultraviolet-absorbing spot on paper chromatography and on paper electrophoresis (Whatman No. 54 paper, acetate buffer pH 4·8). The yield was 31·2 mg. (37%). A solution of the lithium salt was absorbed on a small Dowex-50 column (hydrogen form; 1 cm. × 0·5 cm.$^2$). The aqueous eluate from the column was freeze-dried, to give *cytidine-5′ pyrophosphate* as a colourless glass (Found: C, 24·9; H, 4·2; N, 9·2. $C_9H_{15}O_{11}N_3P_2,2H_2O$ requires C, 24·6; H, 4·3; N, 9·6%).

An experiment on a somewhat larger scale gave a 42% yield of lithium salt.

We thank the Royal Commission for the Exhibition of 1851 for the award of a Senior Studentship which enabled one of us (C. B. R.) to participate in this work.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 3rd,* 1957.]

XUM

## 105. *Mesomorphism and Chemical Constitution. Part X.* The* 2-p-n-*Alkoxybenzylideneaminophenanthrenes and Evidence for the Planarity of the Diphenyl Ring System in the Mesomorphic State.*

By G. W. Gray.

Thirteen anils derived from *p-n*-alkoxybenzaldehydes and 2-aminophenanthrene have been prepared and their mesomorphic properties studied. The series is typical of many, but by comparison of the mesomorphic thermal stabilities with those of the 4-*p-n*-alkoxybenzylideneaminodiphenyls more evidence is obtained for the planar configuration of diphenyl in the mesophases of its derivatives.

The homologous series of anils, the melting points and mesomorphic transition temperatures of thirteen members of which are shown in Table 1, exhibits no unusual features, and the plot of the mesomorphic–isotropic transition temperatures against the number of carbon atoms in the alkyl chain shows the usual alternations, *i.e.*, two falling curves

Table 1. 2-p-n-*Alkoxybenzylideneaminophenanthrenes.*

| | Temp. of transition to | | | | Temp. of transition to | | |
|---|---|---|---|---|---|---|---|
| Alkyl | smectic | nematic | isotropic | Alkyl | smectic | nematic | isotropic |
| Methyl ..... | — | 155° | 213·5° | Octyl ..... | 103° | 140° | 186·5° |
| Ethyl ..... | — | 152·5 | 217 | Nonyl ..... | 120 | 148·5 | 181 |
| Propyl ..... | — | 152·5 | 200·5 | Decyl..... | 121 | 154 | 179·5 |
| Butyl ..... | — | 121·5 | 204 | Dodecyl ..... | 109 | 161 | 173 |
| Pentyl ..... | (<90°) | 132·5 | 193 | Hexadecyl ... | 99·5 | — | 161 |
| Hexyl ..... | (111) | 113 | 194·5 | Octadecyl ... | 108 | — | 156 |
| Heptyl ..... | 116·5 | 129·5 | 187 | | | | |

can be drawn through the points, the upper one for those anils with an even number of carbon atoms in the alkyl chain, and the lower for those with an odd number. The single curve on which the smectic–nematic transition points lie rises very steeply at first, and the smectic mesophases of the pentyl and hexyl ethers are monotropic. The nematic–smectic transition temperature of the pentyl ether cannot be determined accurately as the nematic mesophase does not supercool sufficiently. The curve gradually levels out as the alkyl chain lengthens, and coincides with the upper transition-point curve between the points for the dodecyl and the hexadecyl ether. The m. p.s along the homologous series are irregularly disposed.

The relative mesomorphic thermal stabilities of the *p-n*-alkoxybenzylidene derivatives of 4-aminodiphenyl and 2-aminofluorene and of the di-(*p-n*-alkoxybenzylidene) derivatives of benzidine and 2 : 7-diaminofluorene have already been discussed.[1] The relative mesomorphic behaviours of these series indicate that the diphenyl ring system is planar and denied freedom of rotation about the 1–1′-bond in the mesomorphic states of its compounds. In the anils derived from 2-aminophenanthrene, the phenanthrene nucleus is planar, so the mesomorphic thermal stabilities of the 2-*p-n*-alkoxybenzylideneaminophenanthrenes should provide an interesting comparison with the 4-*p-n*-alkoxybenzylideneaminodiphenyls, and may give more evidence for the planarity of diphenyl in its mesophases, work on which is in progress.

Before considering the average mesomorphic transition temperatures used later as a measure of the relative mesomorphic thermal stabilities of the two series of anils, we will discuss the probable effect on the thermal stability of the smectic phase of changing from the assumedly planar diphenyl ring system to the planar phenanthrene one. The thermal

* Part IX, Gray and Ibbotson, *J.*, 1957, 3228.

[1] Gray, Hartley, Ibbotson, and Jones, *J.*, 1955, 4359; see also Part IX.

stability of the smectic phase depends upon the ability of the molecules to maintain themselves, against the disordering influences of thermal vibration, orientated parallel with their ends in line. A close packing of the molecules, together with permanent reinforcing dipoles acting across the long molecular axes, will therefore favour the formation of a thermally stable smectic phase. If the introduction of a suitable substituent increases the molecular breadth or thickness, then, provided that the atom–substituent dipole is not large enough to counteract this effect, the increased intermolecular separation will reduce the intermolecular forces. The molecules will now be able to move from the smectic layers at a lower temperature, and the compound will be less likely to exhibit a smectic phase. Since the phenanthrene ring system is broader than that of diphenyl and has no permanent dipole moment, anils of the former should be less thermally stable than those of the latter in the smectic phase. The order of this predicted decrease is shown by comparing the average smectic–nematic transition temperatures of the hexyl–decyl ethers of the 2-aminophenanthrene and 4-aminodiphenyl anils; the average in the diphenyl series is 153·5°, and in the phenanthrene 136·6°. The decrease in smectic thermal stability from diphenyl to phenanthrene is therefore 16·9°. Now if there were rotational freedom about the 1–1′-bond in diphenyl, the result would be equivalent to a molecular thickening which should interfere seriously with the closeness of the molecular packing and reduce markedly the lateral intermolecular cohesions in the smectic layers. Since it is difficult to imagine that such non-planar diphenyl anil molecules could produce smectic phases having an average smectic thermal stability 16·9° greater than those of the necessarily planar phenanthrene anil molecules, the smectic phases of the diphenyl anils are probably more thermally stable because the molecules are planar and lath-shaped, whilst the planar phenanthrene molecules give a lower smectic stability as a result of their greater molecular breadth.

To obtain the relative stabilities of the nematic phase, the nematic–isotropic transition temperatures of the methyl–decyl ethers of the phenanthrene and diphenyl anils have been averaged, being 195·6° for the former and 169·2° for the latter, a difference of 26·4°.

The phases of the diphenyl anils are now less stable than those of phenanthrene, reversing the order of stability of the smectic phases. A rotational freedom about the 1–1′-bond in diphenyl might commence in the less highly ordered molecular arrangement of the more mobile nematic phase, and this could account for the lower nematic thermal stability of the diphenyl compounds, but in the light of comparisons already made between mesomorphic mono- and di-anils derived from diphenyl and fluorene,[1] this rotation is unlikely in the nematic phase. For example, it would not be possible to explain the greater nematic thermal stability of di-(*p*-alkoxybenzylidene) derivatives of benzidine than of those of 2 : 7-diaminofluorene. We emphasise that the thermal stability of the nematic phase will not depend solely upon the residual lateral cohesive forces, but also upon the terminal cohesions between molecules. Therefore, increases in breadth, which decrease smectic phase thermal stability, are always less effective in reducing the thermal stability of the nematic phase, so that the breadth of the phenanthrene nucleus is a less important factor when considering the nematic phase. Moreover, the phenanthrene anils will have a higher molecular polarisability than the diphenyl anils in the direction of the major axes of the molecules, as can be inferred from the high double-bond order of the 9 : 10-bond in phenanthrene and the exaltations of molecular refraction,[2] which are 5·53 c.c. and 1·8 c.c. for phenanthrene and diphenyl respectively. Because of the greater conjugation, the terminal intermolecular cohesions should therefore be higher for the phenanthrene anils. It seems more likely that this effect explains the high nematic thermal stability of these compounds, rather than that the diphenyl anils have a low nematic thermal stability because of deviations from planarity.

These results for the phenanthrene anils substantiate previous evidence indicating that diphenyl is planar in the mesomorphic states of its derivatives. From a consideration

[2] Syrkin and Dyatkina, "Structure of Molecules," Butterworths Scientific Publications, London, 1950, p. 203.

of the potential energies of the phases, this configuration is indeed the most probable. In both phase types, the molecular ordering will minimise the potential energy, the more highly ordered smectic phase having the lower potential energy. Any rotational freedom which increases the molecular dimensions and reduces intermolecular cohesion will therefore increase the potential energy of the mesophase. Thus there will be a potential-energy barrier to such a rotation, particularly in the smectic phase and, whereas the terminal methyl group of the alkyl chain can rotate since this would have little effect on the overall cohesive forces in the mesophase, the rotation of one of the rings in diphenyl should be hindered because of the substantial increase in molecular thickness. The smectic phase would be most affected, but the nematic thermal stability would also be reduced (*a*) by the reduction in residual lateral cohesions and (*b*) by the reduction in conjugation between the two aromatic rings.

## Experimental

M. p.s are corrected for exposed stem.

*Determination of Transition Temperatures.*—The m. p.s and the monotropic and enantiotropic mesomorphic transition temperatures were determined in the usual way, with an electrically heated microscope block [3] in conjunction with a projection system.[4] The smectic phases of the anils did not show well-defined focal-conic groups when mounted in thin sections between a glass slide and cover slip, and the samples always exhibited large homœotropic areas. When the cover slip was slightly displaced, complete homœotropy would often result, and the small regions of focal-conic groups would be destroyed. The nematic phases of the anils were readily distinguished by their typical threaded textures.

*Materials.*—2-Acetylphenanthrene, together with the 3-isomer, was prepared by Friedel–Crafts reaction on phenanthrene (m. p. 99°) as described by Mosettig and van de Kamp,[5] who record a yield of 63·5% of 3- (m. p. 72°) and 15% of 2-acetylphenanthrene (m. p. 143°). We used their second method to purify the crude 2-acetylphenanthrene, involving two vacuum distillations followed by crystallisation from benzene. The yields were lower than those reported: 10—11% of the 2- (m. p. 142—143°) and 45—46% of the 3-isomer (m. p. 71—72°).

*2-Acetylphenanthrene oxime.* The mixture of *cis* and *trans* oximes (m. p. 190—193°) was obtained in 98% yield by Bachmann and Boatner's method.[6]

*2-Aminophenanthrene.* The mixture of 2-acetamidophenanthrene and *N*-methyl-2-phenanthramide obtained by Beckmann rearrangement of the isomeric oximes was hydrolysed and separated into the acid and the amine as described by Bachmann and Boatner.[6] These authors claim that the 2-aminophenanthrene is almost pure (m. p. 85°) as precipitated from the hydrolysate and that the yield from the ketone is 81—82%, but our yields were lower (65%) and the product (m. p. 80—83°) contained a high-melting impurity. This was removed by hot filtration, and crystallisation from light petroleum (b. p. 100—120°) gave colourless crystals of 2-aminophenanthrene, m. p. 84—85° [6,7] (52—53%).

Table 2. 2-p-n-*Alkoxybenzylideneaminophenanthrenes.*

| | Found (%) | | | Required (%) | | | Found (%) | | | Required (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Alkyl | C | H | Formula | C | H | Alkyl | C | H | Formula | C | H |
| Me ..... | 85·1 | 5·5 | $C_{22}H_{17}ON$ | 84·9 | 5·5 | $C_9H_{17}$ | 84·9 | 7·4 | $C_{29}H_{31}ON$ | 85·1 | 7·6 |
| Et ..... | 84·8 | 5·9 | $C_{23}H_{19}ON$ | 84·9 | 5·8 | $C_9H_{19}$ | 84·9 | 7·5 | $C_{30}H_{33}ON$ | 85·1 | 7·8 |
| Pr$^n$ ..... | 84·8 | 5·9 | $C_{24}H_{21}ON$ | 85·0 | 6·2 | $C_{10}H_{21}$ | 85·1 | 8·2 | $C_{31}H_{35}ON$ | 85·1 | 8·0 |
| Bu$^n$ ... | 85·2 | 6·6 | $C_{25}H_{23}ON$ | 85·0 | 6·5 | $C_{12}H_{25}$ | 85·4 | 8·2 | $C_{33}H_{39}ON$ | 85·1 | 8·4 |
| $C_5H_{11}$ | 85·0 | 6·8 | $C_{26}H_{25}ON$ | 85·0 | 6·8 | $C_{16}H_{33}$ | 85·2 | 9·0 | $C_{37}H_{47}ON$ | 85·2 | 9·0 |
| $C_6H_{13}$... | 85·0 | 7·2 | $C_{27}H_{27}ON$ | 85·0 | 7·1 | $C_{18}H_{37}$ | 85·3 | 9·4 | $C_{39}H_{51}ON$ | 85·2 | 9·3 |
| $C_7H_{15}$... | 85·2 | 7·5 | $C_{28}H_{29}ON$ | 85·1 | 7·3 | | | | | | |

2-p-n-*Alkoxybenzylideneaminophenanthrenes.*—The anils were prepared by dissolving 2-aminophenanthrene (0·2 g.) in absolute ethyl alcohol (25 ml.), and adding a 10% molar excess of the *p*-alkoxybenzaldehyde, with a few drops of glacial acetic acid as catalyst. The

[3] Gray, *Nature*, 1953, **172**, 1137.
[4] Gray and Ibbotson, *Nature*, 1955, **176**, 1160.
[5] Mosettig and van de Kamp, *J. Amer. Chem. Soc.*, 1930, **52**, 3707.
[6] Bachmann and Boatner, *J. Amer. Chem. Soc.*, 1936, **58**, 2099.
[7] Kunz and Werner, *Ber.*, 1901, **34**, 2524.

anils were rapidly precipitated, but the mixture was warmed on the water-bath for 15 min. to complete the reaction. Sufficient alcohol was then added to dissolve the anils at the b. p., and the crystalline products were isolated on cooling. The anils were pure after two further crystallisations from an equal volume mixture of benzene and light petroleum (b. p. 40—60°). The m. p.s and transition temperatures are in Table 1 and the combustion analyses in Table 2.

The author thanks the Distillers Co. Ltd. and Imperial Chemical Industries Limited for grants.

THE UNIVERSITY, HULL. [*Received, October 9th*, 1957.]

## 106. *Chaksine. Part I.*

By AHMAD KAMAL and GEORG HAHN.

It is suggested that chaksine, $C_{11}H_{21}O_3N_3$, has a guanidine structure, which accounts for all the nitrogen.

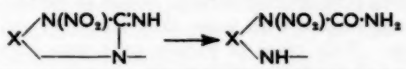
CHAKSINE, an alkaloid from the seeds of *Cassia absus* Linn., was isolated and tentatively assigned the formula $C_{12}H_{21}O_2N_3$ by Ahmad and Siddiqui.[1] Later, the formula $C_{11}H_{21}O_3N_3$ was suggested by Kapur *et al.*[2] and was accepted by the former authors who considered chaksine to be a quaternary base because it absorbs carbon dioxide from the atmosphere and forms salts by replacement of a hydroxyl group. The present authors have confirmed the latter formula by analyses of some more salts (including oxygen determinations), which indicate either a second basic nitrogen atom or formation of an oxonium salt, there being only one strongly basic nitrogen atom.

Siddiqui and Sharma,[3] and Kapur *et al.*,[2] observed that ammonia is liberated when chaksine is heated with alkali. The present authors found that two molecules of ammonia and one of carbon dioxide were evolved when chaksine was heated with an excess of aqueous barium hydroxide. The first molecule of ammonia is set free within 40 hr.; evolution of the second takes at least 240 hr. The remainder of the molecule afforded at least three barium salts, the constitution of which is under investigation. A urea or a guanidine structure is therefore suggested for chaksine.

Treating chaksine with hot nitric acid in concentrated sulphuric acid gave a substance $[C_{11}H_{19}O_2N_3(NO_2)]_2SO_4$, identical with nitrochaksine sulphate which Guha and Ray[4] got by treating chaksine nitrate with ice-cold sulphuric acid. They considered this reaction analogous to the formation of nitrourea from urea nitrate. The present authors consider it more similar to the transformation of guanidine nitrate into nitroguanidine. Moreover, they found, in contradistinction to Guha *et al.*,[3] that nitrochaksine sulphate is not stable to hot water. Heating aqueous nitrochaksine sulphate at 100° causes hydrolysis, with liberation of sulphuric acid while the strongly basic starting material is transformed into an amphoteric acid of weak basicity. This compound appears from analyses to be $C_{11}H_{20}O_5N_4$. Its hydrochloride is hydrolysed in cold water; a sodium salt is formed by sodium carbonate.

Since chaksine does not afford nitrogen with nitrous acid it does not contain a primary amino-group.

The hydrolysis of nitrochaksine sulphate is not intelligible on the basis of a quaternary group in association with an urea group; the tentative guanidine structure for nitrochaksine sulphate permits hydrolysis to an amphoteric compound by the reaction:




[1] Ahmad and Siddiqui, *J. Indian Acad. Sci.*, 1935, **2**, 421.
[2] Kapur, Gaind, Narang, and Ray, *J. Indian Chem. Soc.*, 1940, **27**, 281.
[3] Siddiqui and Sharma, personal communication.
[4] Guha and Ray, *J. Indian Chem. Soc.*, 1956, **33**, 225.

XUM

## Experimental

*Chaksine Salts.*—(*a*) Chaksine sulphate (1·37 g.) was dissolved by heat in water (7 ml.) containing sodium nitrate (2 g.). On cooling, chaksine nitrate was obtained as colourless prismatic needles (1·15 g.), m. p. 218—220°.

Chaksine sulphate (0·54 g.) dissolved when heated in nitric acid (*d* 1·4) for a few minutes on the water-bath. Dilution and cooling gave *chaksine nitrate* (0·45 g.), $[\alpha]_D^{34}$ +43·9° in 1% aqueous solution (Found: C, 46·0; H, 7·1; O, 27·5; N, 19·25. $C_{11}H_{20}O_5N_4$ requires C, 45·8; H, 6·9; O, 27·8; N, 19·4%).

(*b*) Chaksine sulphate (0·11 g.) was dissolved in water (8 ml.) containing sodium nitrite (1 g.) by heating to the b. p. The solution became turbid while hot and desposited crystals on cooling. *Chaksine nitrite* was obtained as prismatic needles (0·086 g.), m. p. 210°, $[\alpha]_D^{30}$ +40·9° in approx. 2% aqueous solution (Found: C, 48·2; H, 7·6; O, 23·6; N, 20·2. $C_{11}H_{20}O_4N_4$ requires C, 48·5; H, 7·35; O, 23·5; N, 20·5%).

(*c*) Chaksine carbonate (0·51 g.) and phosphoric anhydride (0·8 g.) were heated at 120° for 1·25 hr. Water was added and the yellowish-brown precipitate (0·8 g.) collected and washed with water. Extraction with water gave a small quantity of *chaksine phosphate*. Heating the amorphous powder for 7 hr. at 150° gave a further quantity (0·38 g.) as needles, m. p. 162° (Found: C, 40·8; H, 7·0; N, 13·7. $C_{11}H_{20}O_2N_3.H_2PO_4$ requires C, 40·9; H, 6·8; N, 13·0%).

(*d*) Chaksine sulphate (2·74 g.) was dissolved in concentrated sulphuric acid (5 ml.), the temperature rising to 50—60°. The colourless solution was heated on the water-bath for 4 min. at ≯75°. Cooling in ice and addition of ethyl alcohol (10 ml.) precipitated a 1 : 1 *sulphate*. When washed with dioxan this formed broad prism (1·42 g.), m. p. 194—196°, $[\alpha]_D^{22}$ +61 1° in 0·45% solution in 82% sulphuric acid (Found: C, 40·8; H, 6·7; O, 29·5; N, 12·6; S, 9·8. $C_{11}H_{21}O_6N_3S$ requires C, 40·86; H, 6·50; O, 29·72; N, 13·0; S, 9·73%).

This sulphate (0·754 g.) was heated on water-bath with water (10 ml.) for a few minutes. Chaksine sulphate (0·62 g.) was obtained, of m. p. and mixed m. p. 318° (decomp.), $[\alpha]_D^{28}$ +60·6° in 0·29% aqueous solution.

(*e*) Chaksine nitrate (0·29 g.) was dissolved in nitric acid (*d* 1·4; 3 ml.) with slight warming. On cooling, needles of a 1 : 1 *nitrate* crystallised. This (0·21 g.) had m. p. 156° (decomp.) and in water regenerated the usual nitrate (Found: C, 37·0; H, 6·1. $C_{11}H_{21}O_8N_5$ requires C, 37·6; H, 5·95%).

*Nitrochaksine Sulphate.*—Chaksine sulphate (5·48 g.) was dissolved in sulphuric acid (*d* 1·84; 10 ml.), the temperature rising to about 50°. After cooling, nitric acid (*d* 1·4; 5 ml.) was added. Heating on the water-bath caused reaction and the temperature was kept at 80° for 30 min. Cooling and dilution then afforded *nitrochaksine sulphate* as prismatic needles (0·64 g.). Recrystallised from water at <80° these had m. p. 186°, $[\alpha]_D^{31}$ +67·4° in 0·45% solution in concentrated sulphuric acid (Found: C, 40·4; H, 6·4; O, 30·4; N, 17·25; S, 4·9. $C_{22}H_{38}N_8O_{12}S$ requires C, 41·4; H, 6·95; O, 30·1; N, 17·55; S, 5·2%). Material prepared by Ray and Guha's method [3] had, after crystallisation, the same m. p. and [α].

*Hydrolysis of Chaksine.*—Chaksine sulphate (5·480 g.) was heated with barium hydroxide octahydrate (18·9 g.) in water (100 ml.). Ammonia evolved was carried in a stream of carbon dioxide-free nitrogen into 2N-hydrochloric acid, but water carried over was returned to the reaction mixture. In two experiments, (*a*) 2·6009 g. of crude ammonium chloride were recovered after 280 hr., and (*b*) 2·1391 g. after 300 hr. The 2·6009 g. were dissolved in water; the solution, submitted to Kjeldahl analysis, appeared to contain 2·1720 g. of ammonium chloride (theor. for 2 mols., 2·1400 g.). The second batch of this salt contained 2·1% of carbon, whence it is concluded that the content of methylamines is negligible.

The original reaction mixture was treated at the b. p. with 98% sulphuric acid, and the carbon dioxide was carried over in nitrogen into 50% potassium hydroxide solution. The increase in weight indicated 0·7135 g. of carbon dioxide (theor. for 1 mol., 0·8800 g.).

The reaction mixture was then treated with an excess of carbon dioxide and filtered from barium carbonate [which was washed with water (5 × 100 ml.)], and the washings and filtrate were evaporated separately. Four crops of barium salts were obtained which on treatment with oxalic acid gave four acids (under investigation).

*Hydrolysis of Nitrochaksine Sulphate.*—When the sulphate (0·3923 g.) was heated with water (40 ml.) at 100°, the pH fell from 6·0 to 3·0 in 2 hr. After 8—10 hours' heating (pH 2·5) precipitation of crystals began. After 36 hr. the crystals were collected and recrystallised from

water to alcohol. The *product* (yield up to 56%), m. p. 201° (decomp.) (Found: C, 46·35; H, 7·4; O, 27·55; N, 18·4. $C_{11}H_{20}O_5N_4$ requires C, 45·8; H, 6·9; O, 27·8; N, 19·45%), dissolved in 2N-sodium carbonate; concentration of this solution gave a sodium salt. Hydrochloric acid afforded a solid salt which was hydrolysed in water.

Microanalyses were by A. Bernhardt, Max-Planck Institute fur Kohleforschung, 22a Mulheim (Ruhr), West Germany. Substances were dried ($P_2O_5$) at 50° in a high vacuum before analysis.

CENTRAL LABORATORIES, PAKISTAN COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH, KARACHI, PAKISTAN. [*Received, January 28th*, 1957.]

---

## 107. *Alicyclic Diketones and Diols. Part I.* cis- *and* trans-2 : 2 : 5 : 5-*Tetramethylcyclohexane*-1 : 3-*diol.*

By A. W. ALLAN, R. P. A. SNEEDEN, and (in part) J. COLVIN.

An improved method of preparing *cis*- and *trans*-2 : 2 : 5 : 5-tetramethyl-*cyclo*hexane-1 : 3-diol is described. The two diols have been characterised by a number of acyl derivatives from which, contrary to Hirsjarvi's findings,[1] the respective parent diols are regenerated on hydrolysis. Again contary to Hirsjarvi's views, the low-melting diol is shown to be the *trans*-isomer by resolution through the bis-(−)-menthoxyacetates.

HIRSJARVI [1] reported the preparation of two isomeric 2 : 2 : 5 : 5-tetramethyl*cyclo*hexane-1 : 3-diols, m. p. 205—206° and 107—108° respectively, by the electrolytic reduction of 2 : 2 : 5 : 5-tetramethyl*cyclo*hexane-1 : 3-dione (dimethyldimedone) to 3-hydroxy-2 : 2 : 5 : 5-tetramethyl*cyclo*hexan-1-one ,and reduction of the latter with sodium amalgam. The diols were obtained in low overall yield by fractional crystallisation of the resultant mixture.

In the present work the mixed isomeric diols were obtained, in good yield, by reducing dimethyldimedone with lithium aluminium hydride. An initial crystallisation gave substantially pure diol A (m. p. 205—206°). Acetylation of the residue from diol A and chromatography gave a crystalline diacetate which on hydrolysis gave pure diol B (m. p. 107—108°) in low overall yield. Benzoylation of the residue from diol A and chromatography gave two crystalline dibenzoates. The first was identical with diol B dibenzoate and gave diol B on hydrolysis (Hirsjarvi [1] states that diol B dibenzoate gives diol A on hydrolysis). The second was identical with diol A dibenzoate and gave diol A on hydrolysis. On a larger scale the two diols could be separated by fractional crystallisation.

The m. p.s of the diol esters found in the present work agree closely with those reported by Hirsjarvi [except that the di(hydrogen phthalate) was obtained crystalline for the first time]. Hirsjarvi, arguing from the melting points and solubilities of the diols and their derivatives (see Table) assigned the (±)-*trans*-structure to the higher-melting diol, but his attempts to corroborate this by chemical evidence and by optical resolution were unsuccessful. Similarly in the present work, neither di(hydrogen phthalate) gave crystalline diastereoisomers with quinine, brucine, or (+)-1-phenylethylamine.[2]

That the low-melting diol, diol B, has the (±)-*trans*-configuration has now been proved by its resolution through the bis-(−)-menthoxyacetates. Diol B, m. p. 107—108°, with (−)-menthoxyacetyl chloride in pyridine gives an oil which from its infrared spectrum and analytical data is a bis-(−)-menthoxyacetate. Chromatography of this material on alumina yielded two waxy esters, m. p. 59°, $[\alpha]_D^{21}$ −76·5° and m. p. 59°, $[\alpha]_D^{21}$ −54·5°.

Hydrolysis of these diastereoisomers gave (−)-, m. p. 134—137°, $[\alpha]_D^{23}$ −19·4°, and (+)-*trans*-2 : 2 : 5 : 5-tetramethyl*cyclo*hexane-1 : 3-diol, m. p. 125—126°, $[\alpha]_D^{23}$ +22·8° respectively.

[1] Hirsjarvi, *Ann. Acad. Sci. Fennicae*, 1946, Series A, **2**, No. 23.
[2] Cf. Rigby, *J.*, 1949, 1588.

That the high-melting diol, A, has the symmetrical *cis*-configuration is confirmed by the fact that it gave a crystalline homogeneous bis-(−)-menthoxyacetate, m. p. 79—80°, $[\alpha]_D^{19}$ −71·69°, unaltered by repeated crystallisation. Hydrolysis of this derivative gave diol A, m. p. 204—207°, $[\alpha]_D^{19}$ 0°.

Differences in reactivity of the diols are under investigation.

## Experimental

Optical rotations were taken in $CHCl_3$.

cis- *and* trans-2 : 2 : 5 : 5-*Tetramethyl*cyclo*hexane*-1 : 3-*diol*.—A suspension of lithium aluminium hydride (2·5 g.) in dry ether (250 c.c.) was heated (2 hr.) under reflux, the returning condensate passing through a thimble containing 2 : 2 : 5 : 5-tetramethyl*cyclo*hexane-1 : 3-dione[3] (8·5 g.). The mixture was then cooled, and excess of lithium aluminium hydride destroyed by ethyl acetate before addition of water and dilute sulphuric acid. Removal of the ether from the dried organic layer resulted in a semi-crystalline residue (7·4 g.) which on crystallisation from chloroform gave 2 : 2 : 5 : 5-tetramethyl*cyclo*hexane-1 : 3-diol A as prisms (2·1 g.), m. p. 205—206° (from benzene) (Found: C, 70·0; H, 11·3. Calc. for $C_{10}H_{20}O_2$: C, 69·7; H, 11·7%).

*Separation via the Diacetates*.—The mixture of diols (4·8 g.) recovered from the chloroform mother-liquors was treated with acetic anhydride in pyridine, and the mixture of isomeric diacetates (5·1 g.) chromatographed on alumina. Elution with light petroleum (b. p. 40—60°) gave one diacetate as prisms [from light petroleum (b. p. 60—80°)], m. p. 64—66° (Found: C, 65·2; H, 9·2. Calc. for $C_{14}H_{24}O_4$: C, 65·6; H, 9·4%).

The diacetate (900 mg.) on hydrolysis with potassium hydroxide (0·4 g.) in water (5 c.c.) and methanol (25 c.c.) gave the second diol (B) as prisms (100 mg.) [from light petroleum (b. p. 60—80°)], m. p. 107—108° (Found: C, 69·7; H, 11·5%).

*Separation via the Dibenzoates*.—Benzoylation of the residue from diol A in the usual manner gave a semicrystalline mass, which (27 g.) was chromatographed on alumina (500 g.). The product (14 g.) eluted with light petroleum (b. p. 60—80°) was the dibenzoate B, plates, m. p. and mixed m. p. 112—114° (from methanol); a second product (1·57 g.) was the dibenzoate A, prisms, m. p. and mixed m. p. 111—112° (from methanol), sharply depressed on admixture with dibenzoate B. On hydrolysis with aqueous-methanolic potassium hydroxide the dibenzoate of m. p. 112—114° gave diol B, m. p. 107—108°, and the dibenzoate of m. p. 111—112° gave diol A, m. p. 205—206°, neither m. p. being depressed on admixture with the appropriate diol.

*Separation by Crystallisation*.—The crude reduction product from dimethyldimedone (33·6 g.) in ether was concentrated to 1 l.; crystals of diol A (6·55 g.), m. p. 203—205°, were removed and the filtrate concentrated to 300 c.c.; a second crop of diol A (0·43 g.), m. p. 205—206°, was obtained. The ether was removed from the filtrate, and the residue crystallised from acetone. Subsequent fractional crystallisation from acetone–light petroleum (b. p. 40—60°) gave diol B (12·28 g.), m. p. 107—108°. The m. p. of the diols and their derivatives as prepared in the present work and those reported by Hirsjarvi are tabulated.

| | Diol | Diacetate | Dibenzoate | Di(hydrogen phthalate) |
|---|---|---|---|---|
| Diol A ..... | 205—206° | 83·5—84·5° | 110·5—111° | 208—209° (H) |
| | 205—206 [a] | 84—85 [c] | 111—112 [d] | 207—210 [b] (*) |
| Diol B ..... | 107—108 | 64—65 | 111—111·5 | 151—153 (H) |
| | 107—108 [b] | 64—66 [c] | 112—114 [c] | 193—194 [b] (*) |

(*) Present work. (H) Hirsjarvi.[1] Solvents: [a] Benzene; [b] acetone–light petroleum (b. p. 40—60°); [c] light petroleum (b. p. 60—80°); [d] methanol; [e] acetone–methanol.

*Diol B Di(hydrogen Phthalate)*.—Diol B (1 g.) and phthalic anhydride (1·8 g.) in pyridine (3 c.c.) were heated on a steam-bath for 3 hr., set aside overnight, poured into aqueous sodium carbonate, and extracted three time with ether; the aqueous layer was acidified with concentrated hydrochloric acid, and the product isolated with the aid of ether. The *diester* crystallised from acetone–light petroleum (b. p. 40—60°) as prisms, m. p. 193—194° (Found: C, 66·9; H, 6·3. $C_{26}H_{28}O_8$ requires C, 66·65; H, 6·0%).

[3] Halsall and Thomas, *J.*, 1956, 2431.

XUM

*Diol B Bis-(−)-menthoxyacetates.*—(−)-Menthoxyacetyl chloride (20·2 g.) was added slowly to a cooled solution of diol B (6 g.) in pyridine (25 c.c.), and the whole kept overnight. The product (15·5 g.) isolated with the aid of ether was a mixture of the diastereoisomeric bis-(−)-menthoxyacetates of diol B, b. p. 210°/0·1 mm. (Found: C, 72·6; H, 10·7. Calc. for $C_{34}H_{60}O_6$: C, 72·3; H, 10·7%). The infrared spectrum (liquid film) showed no absorption in the OH region and an ester band at 1743 cm.$^{-1}$.

The above derivative was chromatographed on alumina; elution with *n*-hexane gave a viscous oil (5·97 g.), $[\alpha]_D^{20}$ −66·37°, and elution with ether gave a second viscous oil (6·33 g.), $[\alpha]_D^{20}$ −59·02°. The ether eluate was rechromatographed on alumina, and from the similarities in the rotation of successive eluates they were combined into three main fractions: (1) 0·96 g., $[\alpha]_D^{17}$ −71·3°; (2) 1·3 g., $[\alpha]_D^{17}$ −64° to −68°; (3) 1·20 g., $[\alpha]_D^{17}$ −56·5°. Fraction (2) was combined with the original hexane eluate, and the whole rechromatographed on alumina, and from the similarities in the rotation of successive fractions two main eluates were collected: (4) 0·6 g., $[\alpha]_D$ −75·6°, (5) 3·20 g., $[\alpha]_D$ −74° to −58·7°. Fraction (4) set to a wax, m. p. 59°, which could not be crystallised; on distillation one diastereoisomer of the *bis-(−)-menthoxyacetate of diol B*, b. p. 210°/0·1 mm., $[\alpha]_D^{21}$ −76·5° (*c* 0·9), was obtained (Found: C, 72·9; H, 10·8%). The infrared spectrum (liquid film) was identical with that of the original mixture.

Fraction (3) set to a wax, m. p. 59°, which could not be crystallised, but distillation gave the other diastereoisomer of the *bis-(−)-menthoxyacetate* of diol B, b. p. 210°/0·1 mm., $[\alpha]_D^{24}$ −54·5° (*c* 1·1) (Found: C, 72·2; H, 10·8%). The infrared spectrum (liquid film) was identical with that of the original mixture and that of the other diastereoisomer.

*(+)- and (−)-Form of Diol B.*—Hydrolysis of the ester diastereoisomer, $[\alpha]_D^{21}$ −76·5° (0·180 g.), with aqueous-methanolic potassium hydroxide gave crystals (0·018 g.); these on sublimation gave *(−)-diol B*, m. p. 134—137°, $[\alpha]_D^{23}$ −19·4° (*c* 0·5) (Found: C, 69·6; H, 11·5%). The infrared spectrum in $CCl_4$ was identical with that of the racemic diol B.

Hydrolysis of the diastereoisomer, $[\alpha]_D^{21}$ −54·5° (0·633 g.), gave a crystalline product (0·096 g.) and this on sublimation gave *(+)-diol B*, m. p. 125—126°, $[\alpha]_D^{23}$ +22·8° (*c* 0·9) (Found: C, 69·7; H, 11·7%). The infrared spectrum in $CCl_4$ was identical with that of (−)-diol B.

*Diol A Bis-(−)-menthoxyacetate.*—Diol A (1 g.) was treated as described for diol B; the crude product (2·07 g.) solidified. Recrystallisation from acetone–methanol gave the *bis-(−)-menthoxyacetate* as prisms, m. p. 79—80°, $[\alpha]_D^{19}$ −71·69° (*c* 1·1) (Found: C, 72·1; H, 11·1%). The infrared spectrum in Nujol showed no absorption in the OH region and an ester band at 1743 cm.$^{-1}$. The rotation of this derivative did not change with recrystallisation.

*Hydrolysis of Diol A Bis-(−)-menthoxyacetate.*—The derivative (0·25 g.) was hydrolysed with aqueous-methanolic potassium hydroxide, and the product crystallised from chloroform. In this way diol A (0·057 g.) was obtained as prisms, m. p. 204—207°, $[\alpha]_D$ 0°.

One of us (A. W. A.) thanks the Department of Scientific and Industrial Research for a maintenance allowance. All of us thank Dr. G. Eglinton for the infrared spectra and Mr. J. M. L. Cameron for the microanalyses.

THE UNIVERSITY, GLASGOW. [*Received, June 13th*, 1957.]

## 108. *Studies in Co-ordination Chemistry. Part XV.* Complexes of Chromium with a Di(tertiary Arsine).*

By R. S. Nyholm and G. J. Sutton.

Sexicovalent complexes of chromium(III) with *o*-phenylenebisdimethylarsine (I) have been prepared and studied. These are the first complexes of chromium(III) with tertiary arsines to be described. Blue complexes containing one molecule of ligand to each chromium atom have been isolated and shown to be non-electrolytes of the type $[CrDiarsineX_3,H_2O]^0$, where X is a halogen atom. Green compounds having the empirical formula $2CrX_3,3Diarsine$ are considered to be salts of the type $[Cr(Diarsine)_2X_2][CrDiarsineX_4]$; from these salts the perchlorate, $[Cr(Diarsine)_2X_2]ClO_4$, can be prepared readily. The structures have been investigated by using electrical conductivity, cryoscopic, and magnetic measurements. In all the compounds investigated the magnetic moment is approximately 3·9 Bohr magnetons, thus indicating that no electron-pairing has taken place. All attempts to prepare complexes of bivalent chromium with the diarsine were unsuccessful, and no complexes were obtained containing three molecules of ligand co-ordinated to a single chromium atom.

These four papers deal with di(tertiary arsine) complexes of chromium, manganese, ruthenium, and osmium halides. Previous investigations here of the metal complexes of the di(tertiary arsine) chelate group (I) (*o*-phenylenebisdimethylarsine) [1] have been concerned mainly with the metals towards the end of each transition series. To put this work into perspective the abbreviated Periodic Table shown in Table 1 is helpful.

Earlier work [2] showed that the di(tertiary arsine) possesses marked capacity for effecting electron-pairing in transition-metal atoms and for the stabilisation of a wide variety of both common (*e.g.*, $Ni^{II}$) and uncommon (*e.g.*, $Ni^{III}$ and $Ni^{IV}$) valency states.[2] The diamagnetism of $[Ni^{II}(Diarsine)_3][ClO_4]_2$ indicated that electron-pairing different from that expected on the basis of the simple Pauling theory could occur. To study these effects in more detail we examined the complexes of the transition metals with fewer non-bonding *d* electrons—particularly in the two later transition series. As a necessary preliminary, the complexes of the first transition series were examined. This paper deals with Cr complexes; Part XVI with those of Mn, and Parts XVII

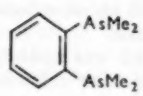
(I) 


Table 1.

| | | | | | |
|---|---|---|---|---|---|
| Cr | Mn | **Fe** | **Co** | **Ni** | **Cu** |
| *Mo* | Tc * † | Ru | **Rh** | **Pd** | *Ag* |
| *W* | *Re* | Os | Ir | **Pt** | **Au** |

* Elements in **bold** type previously investigated; [2] in *italics*, being studied at present; in roman (ordinary) type, being discussed in this Series.
† It is intended to study Tc complexes.

and XVIII with Ru and Os compounds which are compared with those of $Fe^{II}$, $Fe^{III}$, and $Fe^{IV}$ previously reported.

Tervalent chromium is well known to give rise exclusively to sexicovalent complexes

* Part XIV, *J.*, 1952, 3579.

[1] Chatt and Mann, *J.*, 1939, 610.

[2] ($Fe^{II, III}$) Nyholm, *J.*, 1950, 851; ($Fe^{IV}$) Parish and Nyholm, *Chem. and Ind.*, 1956, 470; ($Co^{II, III}$) Nyholm, *J.*, 1950, 2070; ($Ni^{II, III}$) *idem*, *J.*, 1950, 2061; ($Ni^{IV}$) *idem*, *J.*, 1951, 2602; ($Ni^{0, II}$) *idem*, *J.*, 1952, 2906; ($Cu^{I}$) Kabesh and Nyholm, *J.*, 1951, 38; ($Rh^{III}$) Nyholm, *J.*, 1950, 857; ($Pd^{II}$) Chatt and Mann, *J.*, 1939, 1622; Harris, Nyholm, and Stephenson, *Nature*, 1956, 177, 1127; *J.*, 1956, 4375; ($Pt^{II}$) Harris, Nyholm, and Phillips (unpublished); ($Au^{I, III}$) Nyholm, *Nature*, 1951, **168**, 705; Harris, Nyholm, and Stephenson, *Rec. Trav. chim.*, 1956, **75**, 687; Harris and Nyholm, *J.*, 1957, 63.

XUM

when the donor atoms of the ligands are nitrogen and oxygen. These are very stable and react very slowly; as illustrations trisethylenediamine- and trioxalato-chromium(III) ions have been resolved [3] and the $[Cr(H_2O)_6]^{3+}$ ion exchanges [4] the water molecules only very slowly with $H_2{}^{18}O$. In this investigation with the di(tertiary arsine), again $Cr^{III}$ gives rise to sexicovalent complexes only. Since the $Cr^{3+}$ ion has a $(3d_\epsilon)^3$ configuration with two empty $d_\gamma$ orbitals, the formation of an octahedral complex, even with ligands like $CN^-$, is not expected to lead to electron-pairing. However, the $Cr^{2+}$ ion has one more electron and ligands like dipyridyl and the cyanide ion effect a reduction in the number of unpaired electrons from four to two.[5]

No reaction occurs between *o*-phenylenebisdimethylarsine and chromium-(II) or -(III) halides in water or in alcoholic solution when much water is present. When the solvent is only slightly moist, however, combination takes place between chromium(III) halides and the ligand in solvents such as methanol, ethanol, acetone, or dioxan, with formation of slightly soluble *green* complexes having the empirical formula $CrX_3,1\frac{1}{2}$Diarsine and very soluble *blue* compounds of the empirical formula CrDiarsine$X_3$Q, where Q represents one molecule of the solvent, usually water. The reactions are hastened by refluxing in the appropriate solvent or by warming for a few minutes on a water-bath. If the molar proportion of diarsine to chromic salt is in the ratio of 2 : 1, then the less soluble green complexes are preferentially obtained, whilst equimolecular proportions favour the formation of the soluble blue compounds. By refluxing an alcoholic solution of the latter with the diarsine, the less soluble green complexes were obtained. If excess of perchloric acid is added beforehand, perchlorates of the formula $[Cr(Diarsine)_2X_2]ClO_4$ are precipitated. Purification of the perchlorate of the *green* halide complexes is effected readily by adding diethyl ether, in which the blue mono-diarsine complex is readily soluble. After evaporation of this ether solution to dryness under reduced pressure, the bright blue compound can be obtained pure by repetitive extraction with chloroform and precipitation with light petroleum.

*Structure of the Blue Soluble Complexes.*—Since the solvent molecule Q, presumably occupying the sixth co-ordinating position, may be methanol, ethanol, or water, mixed blue complexes usually result unless the solvent used is free from water. Solvents such as acetone yielded blue complexes in which methanol appeared to have partly replaced the water molecule, traces of the former being present in the common solvent acetone. We therefore attempted to form a blue complex by using dioxan as the solvent; the presence of a co-ordinated molecule of this solvent would markedly affect the analysis. Unfortunately, anhydrous chromic salt would not dissolve in this solvent, and a little water was added to assist in the solution. The resulting blue chloro-compound had the composition $[CrDiarsineCl_3(H_2O)]^0$, $H_2O$ completely replacing the dioxan to yield the aquo-complex. The structure of this chloride and of the bromo-derivative was established by conductivity measurements in nitrobenzene in which they are virtually non-electrolytes. Molecular-weight determinations in chloroform show that they are monomeric. The complexes are thus clearly sexicovalent non-electrolytes. Although un-ionised in nitrobenzene, the complexes react readily with silver nitrate in aqueous alcoholic solution to precipitate all of the halogen as silver halides. The properties of the compounds are shown in Table 2. In all cases the magnetic moment is very close to the spin-only value for three unpaired electrons (3·88 B.M.).

*Structure of the Less-soluble Form.*—The empirical formula $CrCl_3,1\frac{1}{2}$Diarsine must clearly be doubled at least, and the complex is then most readily formulated as $[Cr(Diarsine)_2Cl_2][CrDiarsineCl_4]$ or as $[Cr(Diarsine)_3][CrCl_6]$. Treatment of a solution of this salt with perchloric acid yields the salt $[Cr(Diarsine)_2Cl_2]ClO_4$, which reaction seems to favour the first structural formula. Furthermore, the $[CrDiarsineCl_4]^-$ anion

[3] Werner, *Ber.*, 1912, **45**, 3061; see also *ibid.*, 1911, **44**, 3132.
[4] Plane and Taube, *J. Phys. Chem.*, 1952, **56**, 33.
[5] Burstall and Nyholm, *J.*, 1952, 3570.

is apparently related to the soluble blue non-electrolyte complexes. The interconversion presumably occurs according to the reaction

$$[\text{CrDiarsine}Cl_4]^- + H_2O \rightleftharpoons [\text{CrDiarsine}Cl_3(H_2O)]^0 + Cl^-$$

since the formation of the salt-like complex ion on the left of the equation is favoured by the presence of a high concentration of HCl. The trisdiarsine formula is also made improbable because all attempts to prepare a $[\text{CrDiarsine}]_3^{3+}$ ion have been unsuccessful. Prolonged refluxing of the chromic perchlorate in ethanol with excess of the diarsine failed to produce any reaction or change from the purple colour of the hexa-aquochromic

TABLE 2. *Properties of chromium*(III) *di(tertiary arsine) complexes.*

| | | Molecular conductivity in $Ph{\cdot}NO_2$ at 25° | | Magnetic susceptibility and moment at 20° | | | | |
|---|---|---|---|---|---|---|---|---|
| Compound * | Colour | $\Lambda_M$ | Concn. ($10^{-3}$M) | $\chi_g \times 10^{-6}$ | $\chi_M \times 10^{-6}$ | Diamag. corrn. | $\chi_M' \times 10^{-6}$ | $\mu_{eff.}$ (B.M.) |
| $[CrDCl_3,H_2O]^0$ | Bright blue | 0·7 | 6·49 | 12·75 | 5885 | 264 | 6149 | 3·82 |
| $[CrDBr_3,H_2O]^0$ | Deep blue | 0·6 | 4·00 | 10·15 | 6050 | 295 | 6345 | 3·87 |
| $[CrD_2Cl_2][CrDCl_4]$ | Bright green | 40·0 | 0·97 | 10·30 | 12,100 | 699 | 12,799 | 3·88 † |
| $[CrD_2Cl_2]ClO_4$ | Pale green | 28·2 | 2·27 | 7·41 | 5900 | 456 | 6356 | 3·87 |
| $[CrD_2Br_2][CrDBr_4]$ | Dark green | 38·1 | 1·25 | 8·39 | 12,100 | 736 | 12,836 | 3·88 † |
| $[CrD_2Br_2]ClO_4$ | Deep green | 26·9 | 0·71 | 7·02 | 6200 | 477 | 6677 | 3·96 |
| $[CrD_2I_2][CrDI_4]$ | Brown-green | 41·9 | 0·384 | 7·01 | 12,090 | 823 | 12,913 | 3·89 † |
| $[CrD_2I_2]ClO_4$ | Pale green | 26·7 | 1·89 | 6·27 | 6140 | 497 | 6637 | 3·94 |

* D = Ditertiary arsine chelate group, see (I). † Per $Cr^{III}$ atom.

ion; the original diarsine was recovered from the solution. The perchlorate $[Cr(\text{Diarsine})_2Cl_2]ClO_4$ gives a molecular conductivity in nitrobenzene which indicates the expected two ions, and ebullioscopic determination of molecular weight in acetone also supports this, since a value corresponding to almost complete dissociation is obtained. Unfortunately, the low solubilities of the complexes of empirical formula $CrX_3,1\frac{1}{2}$Diarsine prevented determination of their molecular weights. As with the blue non-electrolyte complexes the magnetic moments are again close to the spin-only value for 3 unpaired electrons.

The only puzzling feature is the abnormally high conductivity of the $[Cr(\text{Diarsine})_2X_2]^+[\text{CrDiarsine}X_4]^-$ complexes in nitrobenzene. This must presumably arise from dissociation of the anion in this solvent. This hypothesis finds support from the fact that stable complexes of the $[\text{CrDiarsine}X_4]^-$ anion could not be isolated by using simple cations such as $K^+$. An equilibrium of the type $[\text{CrDiarsine}Cl_4]^- + 2Ph{\cdot}NO_2 \rightleftharpoons [\text{CrDiarsine}Cl_2(Ph{\cdot}NO_2)_2]^+ + 2Cl^-$ is suggested as a possible explanation.

Absorption spectra of all these complexes have been recorded and their significance will be discussed in a later communication dealing with spectra of the di(tertiary arsine) complexes for all the transition metals.

All attempts to obtain halogeno-complexes of the diarsine with chromium(II) were unsuccessful, various solvents having been tried. In a later communication, however, we shall describe mixed di(tertiary arsine)–carbonyl complexes of chromium in which the chromium atom is bivalent. As with certain $Ni^{II}$ complexes it seems to be necessary to start with a carbonyl rather than to attempt direct co-ordination.

## Experimental

*Dichlorodi-(o-phenylenebisdimethylarsine)chromium*(III) *Tetrachloromono-(o-phenylenebis-dimethylarsine)chromate*(III).—Chromic chloride tetrahydrate (0·5 g.) was heated with excess of 10N-hydrochloric acid and evaporated almost to dryness. The purple residue was treated with 10N-hydrochloric acid (5 ml., and the mixture dissolved in acetone (50 ml.) and filtered. Diarsine (1·1 g.) in acetone (10 ml.) was added, and the mixture refluxed for 30 min., then concentrated to 6 ml. Ethyl ether was added with shaking to precipitate the *complex* as a fine green powder. The precipitate was washed well with ether to remove traces of the blue complex and dried *in vacuo* (Found: C, 30·7; H, 4·1; Cl, 18·0. $C_{30}H_{48}Cl_6As_6Cr_2$ requires C, 30·72; H, 4·04; Cl, 18·14%).

*Dichlorodi-(o-phenylenebisdimethylarsine)chromium*(III) *Perchlorate*.—The above procedure was repeated, 30% perchloric acid (2 ml.) being substituted for the 10N-hydrochloric acid. The pale green precipitate which settled out after refluxing with diarsine and the addition of ethyl ether was washed several times with ether and dried *in vacuo* [Found: C, 30·1; H, 4·1; Cl(chloro), 9·27%; *M*, ebullioscopic in 2·12% solution in acetone, 377. $C_{20}H_{32}O_4Cl_2As_4Cr$ requires C, 30·13; H, 4·06; Cl(chloro), 8·9%; *M*, 795].

*Dibromodi-(o-phenylenebisdimethylarsine)chromium*(III) *Tetrabromomono-(o-phenylenebisdimethylarsine)chromate*(III).—The procedure was the same as for the complex $[Cr(Diarsine)_2Cl_2][CrDiarsineCl_4]$, except that lithium bromide (3 g.) in ethanol was added before refluxing in acetone, and hydrobromic acid substituted for hydrochloric acid in the initial stages (Found: C, 25·2; H, 3·4; Br, 33·5. $C_{30}H_{48}Br_6As_6Cr_2$ requires C, 24·97; H, 3·32; Br, 33·3%).

*Dibromodi-(o-phenylenebisdimethylarsine)chromium*(III) *Perchlorate*.—The above experiment was repeated except that lithium bromide was omitted and 30% perchloric acid (2 ml.) added before refluxing in acetone (Found: C, 27·1; H, 3·7; Br, 18·1%; *M*, ebullioscopic in 1·42% solution in acetone, 342. $C_{20}H_{32}O_4ClBr_2As_4Cr$ requires C, 27·19; H, 3·65; Br, 18·1%; *M*, 884).

*Di-iododi-(o-phenylenebisdimethylarsine)chromium*(III) *Tetraiodomono-(o-phenylenebisdimethylarsine)chromium*(III).—Hydriodic acid and lithium iodide (3·0 g.) were substituted for lithium bromide and hydrobromic acid, and the rest of the procedure was as for the corresponding bromo-complex (Found: C, 21·0; H, 2·9; I, 43·3. $C_{30}H_{48}I_6As_6Cr_2$ requires C, 20·90; H, 2·81; I, 44·2%).

*Di-iododi-(o-phenylenebisdimethylarsine)chromium*(III) *Perchlorate*.—By omitting lithium iodide in the last preparation and including hydriodic acid and perchloric acid the pale green *compound* $[Cr(Diarsine)_2I_2]ClO_4$ was obtained. Owing to its appreciable solubility its solution must be made very concentrated before precipitation occurs (Found: C, 24·2; H, 3·1; I, 25·7%; *M*, ebullioscopic in 2·3% solution in acetone, 460. $C_{20}H_{32}O_4ClI_2As_4Cr$ requires C, 24·56; H, 3·29; I, 25·97%; *M*, 978).

*Trichloromonoaquomono-(o-phenylenebisdimethylarsine)chromium*(III).—Chromic chloride tetrahydrate (0·5 g.) and the diarsine (0·55 g.) were dissolved in dioxan (20 ml.), concentrated hydrochloric acid (5 ml.) added, and the mixture refluxed until a deep blue colour had developed. The mixture was then evaporated to 10 ml. on a water-bath under reduced pressure, and filtered. The filtrate was then treated with diethyl ether, stirred, and set aside. The green precipitate of the salt-like form was removed by centrifuging. The supernatant liquor was filtered and evaporated to dryness under reduced pressure; the residue was dissolved in a small quantity of chloroform, a little ether added, and the solution again filtered. The addition of light petroleum to the filtrate resulted in precipitation of the required *product* as a blue powder. The latter was then redissolved in ether, reprecipitated with light petroleum, and dried in a vacuum desiccator (Found: C, 26·2; H, 4·3; Cl, 22·8%; *M*, ebullioscopic in 2·26% solution in chloroform, 424. $C_{19}H_{18}OCl_3As_2Cr$ requires C, 25·97; H, 3·92; Cl, 23·00%; *M*, 462). The substance decomposes without melting between 240° and 245°.

*Tribromomonoaquomono-(o-phenylenebisdimethylarsine)chromium*(III).—The aforementioned procedure was repeated but hydrobromic acid was used instead of hydrochloric acid, and the corresponding *bromo-compound* was formed (Found: C, 19·7; H, 3·2; Br, 40·9%; *M*, ebullioscopic in 4·5% solution in chloroform, 610. $C_{19}H_{18}OBr_3As_2Cr$ requires C, 20·16; H, 3·05; Br, 40·3%; *M*, 596).

William Ramsay and Ralph Forster Laboratories,
University College, London.
School of Applied Chemistry (Granville College),
N.S.W. University of Technology, Sydney.

[*Received, August 7th*, 1957.]

## 109. *Studies in Co-ordination Chemistry. Part XVI.* Complexes of Bivalent and Tervalent Manganese with a Di(tertiary Arsine).*

By R. S. Nyholm and G. J. Sutton.

Complexes of bivalent and tervalent manganese halides with the di(tertiary arsine) chelate group, *o*-phenylenebisdimethylarsine, are described. The bivalent complexes have the general formula $Mn(Diarsine)_2X_2$ where X may be Cl, Br, or I. They are best prepared under anhydrous conditions in 1 : 4-dioxan, and are non-electrolytes and monomeric in nitrobenzene. Magnetic data indicate the presence of five unpaired electrons; hence they can be formulated as spin-free (outer-orbital) sexicovalent complexes of $Mn^{II}$. A red $Mn^{III}$ diarsine of the formula $[MnDiarsineCl_2,H_2O]ClO_4$ containing four unpaired electrons has also been isolated. These are the first complexes of manganese with tertiary arsines to be described. Owing to the case with which the compounds are hydrolysed they are difficult to obtain pure.

In the preceding paper it was shown that chromium(III) but not chromium(II) complexes of the di(tertiary arsine) (I) (p. 560) could be isolated. Special interest attaches to manganese-(II) and -(III) since the formation of any octahedral complex using two $3d_\gamma$ orbitals necessitates electron-pairing, which is very uncommon with the lower-valency states of manganese and has been reported previously only with the complex cyanide.[1] Excepting scandium, which forms no bivalent compounds, bivalent manganese has the lowest total ionisation potential of the first transition elements, and its effective electronegativity is thus the smallest in the series; hence its capacity to form covalent bonds (in the Pauling sense of producing a spin-paired complex) is relatively small. Thus we find that most $Mn^{II}$ complexes which have been described [2] involve co-ordination with ligands of high electronegativity such as oxygen in water and nitrogen in amines, the metal–ligand bond being strongly polar. We might expect difficulty, therefore, in attempting to substitute the di(tertiary arsine) for ligands such as the foregoing.

It was expected that co-ordination might be favoured by heating the reactants under pressure or by the use of a suitable solvent with a low affinity for the $Mn^{2+}$ ion. In the presence of water, methanol, ethanol, or acetone as solvent no evidence of co-ordination of diarsine with the $Mn^{2+}$ ion was observed, presumably owing to the strong bond between the metal and the solvent. Indeed, a large number of $Mn^{II}$ complexes with alcohols such as ethanol,[3] propanol,[4] and glycerol [5] are known. Dioxan was then tried as a possible reaction medium for, although it does form a complex with manganous halides, its low dielectric constant (2·2) and ethereal character suggested that the bond might not be very strong. Furthermore, it is a better solvent for $Mn^{II}$ halides than benzene, ether, or chloroform. In anhydrous dioxan co-ordination of the diarsine with $Mn^{II}$ takes place very readily and the yield is limited only by the low solubility of the manganous halide in this solvent. The manganese(II) halide forms a violet complex with dioxan; addition of diarsine causes an instantaneous loss of colour as the dioxan is displaced. Complexes of the type $Mn(Diarsine)_2X_2$ were thus obtained (in which X = Cl, Br, or I) as white crystalline compounds by keeping the solutions at about 5° for several hours. The chloro-complex was not obtained pure owing to the difficulty in preventing hydrolysis. Similar trouble occurred with the bromo- and the iodo-complex. The complexes can also be

* Part XV, preceding paper.

[1] Goldenberg, *Trans. Faraday Soc.*, 1940, **36**, 847.
[2] Sidgwick, "The Chemical Elements and Their Compounds," Oxford Univ. Press, 1950, p. 1286.
[3] Druce, *J.*, 1937, 1407.
[4] Zvyaginstsev and Chkhenkelei, *J. Gen. Chem. U.S.S.R.*, 1941, **11**, 791 (*Chem. Abs.*, 1942, **36**, 3743).
[5] Gomer and Tyson, *J. Amer. Chem. Soc.*, 1944, **66**, 1331.

formed in diethyl ether, but the method is impracticable owing to the low solubilities of the halides in this solvent. The properties of the various complexes of manganese(II) are given in the Table. The low molecular conductivities in nitrobenzene indicate that the complexes are practically non-electrolytes in this solvent and hence that the $Mn^{II}$ atom is sexicovalent. The molecular weights of the bromide and iodide confirm this. It is apparent from the magnetic moments ($\mu_{eff}$ ~5·9 B.M.) that no electron-pairing occurs and hence that no 3*d* orbitals are involved in the octahedral binding. This is important,

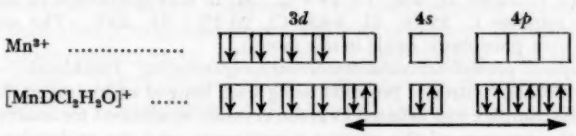
*Properties of manganese diarsine complexes.*

| Compound * | Colour | Molecular conductivity in $PhNO_2$ at 25° $\Lambda_M$ | Concn. ($10^{-3}$M) | Magnetic susceptibility at 20° $\chi_g \times 10^{-6}$ | $\chi_m \times 10^{-6}$ | Diamag. corrn. | $\chi_m' \times 10^{-6}$ | $\mu_{eff.}$ (B.M.) |
|---|---|---|---|---|---|---|---|---|
| $MnD_2Cl_2$ † ..... | White | 3·1 † | 0·54 | 21·9 | 15,300 | 426 | 15,726 | 6·1 † |
| $MnD_2Br_2$ ..... | White | 0·6 | 1·79 | 18·56 | 14,600 | 447 | 15,047 | 5·95 |
| $MnD_2I_2$ ..... | Pale yellow | 1·1 | 1·61 | 16·60 | 14,600 | 467 | 15,067 | 5·96 |
| $[MnDCl_2H_2O]ClO_4$ | Purple-red | 18·2 | 2·27 | 20·6 | 10,920 | 270 | 11,190 | 5·13 |
| $[MnDBr_2H_2O]ClO_4$ | Green | 21·2 | 0·36 | — | — | — | — | — |

* D = Diarsine. † Impure.

because in every previous case where complexes of this di(tertiary arsine) have been prepared spin-pairing with $3d_\gamma$ orbital binding occurs.* We attribute this to the high stability of the half-filled 3*d* sub-shell in the $Mn^{II}$ atom *and* the low electronegativity of the $Mn^{2+}$ ion. The complexes of the isoelectronic tervalent iron atom do show electron-pairing but in this case the higher valency state means that the iron atom has a higher effective electronegativity. This means a greater tendency to draw the lone-pair electrons of the arsenic atoms into the $3d_\gamma$ orbitals.

Attempts to oxidise these bivalent manganese complexes to the tervalent state were unsuccessful. Addition of various oxidising agents such as chlorine or bromine yielded fleeting pink colours suggestive of a higher oxidation state but the complexes immediately decomposed. Hence it was decided to try to cause the diarsine to react directly with suitable anhydrous manganese(III) compounds. The diarsine rapidly reduced both manganic acetate and manganic acetylacetone to the bivalent state even in anhydrous dioxan or in acetic anhydride, but in the presence of a small amount of water a small yield of a red crystalline precipitate of composition $[MnDiarsineCl_2H_2O]ClO_4$ is formed. Since the reduction is the principal reaction, the amount of water required has to be kept to a minimum; it is added by using 70% perchloric acid in conjunction with acetic anhydride and glacial acetic acid as solvent. No loss in weight occurred when this compound was stored over phosphoric oxide for one month, hence it appears that the water is co-ordinated and not zeolitic. All attempts to oxidise or reduce the complex $[MnDiarsineCl_2H_2O]ClO_4$ resulted in loss of diarsine by decomposition. A molecular-weight determination in nitrobenzene gave a result indicating that two ions were formed. Conductivity measurements in nitrobenzene were in agreement with this formulation as a uni-univalent




electrolyte. The magnetic moment of 5·1 B.M. indicates four unpaired electrons, as shown in the diagram. This indicates that only one vacant $3d_\gamma$ orbital is left for bond formation.

* Complexes of $Cr^{III}$ are excluded from this generalisation because in this case two $3d_\gamma$ orbitals are available *without* spin-pairing.

XUM

The co-ordination number of 5 for the $Mn^{III}$ ion suggests the possibility that the bonding orbitals may be $3d4s4p^3$.

By using dry hydrogen bromide in place of hydrogen chloride, very small amounts of a green compound having similar properties to the above were obtained. This is probably the analogous bromo-complex $[MnDiarsineBr_2H_2O]ClO_4$.

All attempts to obtain manganese complexes of the diarsine with the anions cyanide, thiocyanate, sulphate, perchlorate, oxalate, fluoride, and nitrate were unsuccessful. Attempted substitution in the phenanthroline complex $Mn\,phenan_2Cl_2$ was also unsuccessful.

## Experimental

*Dichlorodi-*(o-*phenylenebisdimethylarsine*)*manganese*(II).—Anhydrous manganous chloride was treated with 1 : 4-dioxan (400 ml.) which had been dried (Na) and redistilled. The mixture was stirred, warmed to 50°, and set aside. The anhydrous manganous chloride gradually dissolved owing to the progressive formation of the purple $MnCl_2$–dioxan complex. The solution was then filtered, the amount of residue showing that only a little manganous chloride had dissolved. Diarsine (0·2 g.), dissolved in 5 ml. of dioxan, was added to the filtrate, and the mixture stirred. The colour faded to a white opalescence as diarsine gradually replaced the dioxan, a white precipitate of the complex settling out when the solution was placed in a refrigerator. The substance was separated by decantation and centrifuging, washed with dioxan and ether, and dried *in vacuo*. The white crystalline solid which resulted was deliquescent and always gave analytical figures for carbon and chlorine which were low. The molecular conductivity (see Table) indicated a non-electrolyte with some slight impurity.

*Dibromodi-*(o-*phenylenebisdimethylarsine*)*manganese*(II).—Anhydrous manganous bromide was prepared by dissolving manganous carbonate in hydrobromic acid, evaporating the solution, and heating the residue. The procedure as for the chloride was then repeated with use of manganous bromide, diarsine, and dioxan. The white *complex* (0·1 g.), in the form of rhombic crystals, decomposed at 196° (Found: C, 29·5; H, 3·9; Br, 20·95%; *M*, in 1·6% solution in nitrobenzene, 720. $C_{20}H_{32}Br_2As_4Mn$ requires C, 30·5; H, 4·06; Br, 20·35%; *M*, 787).

*Di-iododi-*(o-*phenylenebisdimethylarsine*)*manganese*(II).—Manganese carbonate was dissolved in iodine-free hydriodic acid. The anhydrous iodide was obtained by driving off the water of hydration in the absence of air. The iodide was treated with diarsine as for the bromide. The pale yellow crystals (0·1 g.) decomposed on heating at 194° (Found: C, 26·3; H, 3·8; I, 29·6%; *M*, in 1·74% solution in nitrobenzene, 770. $C_{20}H_{32}I_2As_4Mn$ requires C, 27·2; H, 3·63; I, 28·8%; *M*, 881).

*Dichloromonoaquo-*o-*phenylenebisdimethylarsinemanganese*(III) *Perchlorate*.—Manganic acetate (1 g.), dissolved in the minimum of absolute alcohol, was cooled to 0°, and 70% perchloric acid (1 ml.) added, together with acetic anhydride (0·2 ml.), giving little more than the stoicheiometric proportion of water required. The solution was saturated with dry hydrogen chloride, and diarsine (0·2 g.) in a little ethanol added cautiously with intermittent shaking until a scarlet colour had developed and silky purplish-red crystals settled out. The mixture was set aside until settling was complete (1 hr.), and the liquid was then separated by centrifuging, and the crystals (0·05 g.), after being washed with a little ethanol and ether, were dried ($CaCl_2$) in a vacuum desiccator. Since the diarsine also reduced the manganese(III) to manganese(II), excess of perchlorate ion was added rapidly to precipitate the complex. The *complex* was soluble in acetone and fairly soluble in ethanol, the latter reducing it on warming to 50°. It is insoluble in common solvents other than nitrobenzene. The crystals had m. p. 202° (decomp.) (Found: C, 22·8; H, 3·5; Cl, 19·8%; *M*, in 0·24% solution in nitrobenzene, 240. $C_{10}H_{18}O_5ClAs_2Mn$ requires C, 22·70; H, 3·43; Cl, 20·2%; *M*, 530). The substance lost no detectable weight over phosphoric oxide in one month.

*Dibromomonoaquo-*o-*phenylenebisdimethylarsinemanganese*(III) *Perchlorate*.—This was prepared as for the chloride, hydrogen bromide being used instead of hydrogen chloride. A very small amount of the complex was isolated as green crystals insufficient for analysis. Qualitative tests established the presence of the various constituents, and the molecular conductivity in nitrobenzene solution was that expected for a univalent electrolyte.

William Ramsay and Ralph Forster Laboratory,
University College, London.
School of Applied Chemistry (Granville College),
N.S.W. University of Technology, Sydney.

[*Received, August 7th*, 1957.]

# 110. *Studies in Co-ordination Chemistry. Part XVII.* Complexes of Ruthenium with a Di(tertiary Arsine).*

By R. S. Nyholm and G. J. Sutton.

Complexes of bivalent and tervalent ruthenium with *o*-phenylenebisdimethylarsine have been prepared and studied. Bivalent ruthenium forms compounds of the general formula $Ru(Diarsine)_2X_2$, where X is a halogen atom. These are diamagnetic and are non-electrolytes in nitrobenzene and hence the ruthenium atom is sexicovalent. Oxidation of these bivalent complexes yields tervalent ruthenium salts containing the cation $[Ru(Diarsine)_2X_2]^+$. Magnetic measurements indicated the presence of one unpaired electron in the tervalent complexes. Attempts to isolate quadrivalent ruthenium derivatives were unsuccessful.

An earlier investigation [1] showed that bivalent and tervalent iron give rise to complexes of the type $[Fe(Diarsine)_2X_2]^0$ and $[FeX_2(Diarsine)_2]ClO_4$ with *o*-phenylenebisdimethylarsine, and recently [2] it has been possible to oxidise the iron(III) complexes to form $[Fe^{IV}Cl_2(Diarsine)_2][ReO_4]_2$, a derivative of quadrivalent iron. The investigation of the ruthenium complexes was prompted mainly by interest in their magnetic behaviour, but also in order to compare the complexes with those of iron and osmium. Special interest attaches to the quadrivalent state since this gives rise to anomalous magnetic behaviour in the case of osmium. An earlier [3] investigation of the complexes of ruthenium with methyldiphenylarsine yielded non-electrolytes of the types $[Ru^{II}X_2,4Ph_2AsMe]^0$ and $[Ru^{III}Cl_3,3Ph_2AsMe]^0$ but the magnetic properties were not investigated. No previous work on the ruthenium complexes of this chelate group has been reported.

*Bivalent Ruthenium Complexes.*—When an alcoholic solution of *o*-phenylenebisdimethylarsine is added to ruthenium(III) halides in aqueous ethanol, and the mixture refluxed for a few minutes, crystals of the compound $[RuX_2(Diarsine)_2]^0$ are precipitated. The diarsine reduces the $Ru^{III}$ to the bivalent stage. As shown in the Table, these compounds vary in colour from pale yellow to orange. In the case of the iodide it was also possible to isolate a purple form by using more concentrated solutions in the original preparation. On heating, the violet form reverts to the orange, and both forms give the same pale yellow solution in chloroform. Addition of light petroleum to this solution yields only the orange form. A possible explanation for the existence of two forms is geometrical isomerism since the two iodine atoms in an octahedral complex could be either *cis* or *trans*.† It was not possible to check this idea by electric dipole-moment measurements owing to the insolubility of the compounds in dioxan and benzene, the two solvents likely to be of value for such a purpose. In nitrobenzene and in acetone, in which the complexes are sparingly soluble, they dissolve to yield the light-coloured form. Ebullioscopic molecular-weight determinations in chloroform and molecular conductivities in nitrobenzene show that the complexes are non-electrolytes. This, together with the diamagnetism, clearly indicates a bivalent ruthenium atom in a sexicovalent, presumably octahedral inner-orbital ($4d^25s5p^3$) complex. The corresponding thiocyanate was also prepared in the hope that it might be more soluble in benzene or dioxan to enable electric dipole-moment measurements to be carried out. Unfortunately, this thiocyanate is also only sparingly soluble. The properties of the compounds are summarised in the Table.

*Tervalent Complexes.*—Potentiometric titrations of the bivalent chlorine complex with

* Part XVI, preceding paper.

† Alternatively—and we think more likely—the purple form might be a salt of the type $[Ru(Diarsine)_3][RuDiarsineI_4]$.

[1] Nyholm, *J.*, 1950, 851.
[2] Nyholm and Parish, *Chem. and Ind.*, 1956, 470.
[3] Dwyer, Humpoletz, and Nyholm, *J. Proc. Roy. Soc. N.S.W.*, 1946, **80**, 217.

potassium dichromate in dilute acid solution show that a one-electron oxidation per ruthenium atom can be effected. Owing to the insolubility of the bivalent complex in water the reaction was carried out in chloroform–acetone. The acetone also ensured that the resulting ruthenium(III) complex remained in solution, since the estimated oxidation–reduction potential for the system $[Ru(Diarsine)_2Cl_2]^0 - e \longrightarrow [Ru(Diarsine)_2Cl_2]^+$ is +0·64 v. This explains how the $Ru^{II}$ complex can be oxidised to the $Ru^{III}$ compound by ferric chloride; also how the $Ru^{III}$ complex ion is reduced by iodide ions.

The ruthenium(III) complexes of the diarsine were prepared conveniently by oxidation of the corresponding ruthenium(II) complexes with chlorine or bromine in chloroform. However, the reactions are complicated by the easy removal of one molecule of the diarsine with the formation of complexes of the type $[Ru(Diarsine)_2X_2][Ru(Diarsine)X_4]$. No corresponding anion of tervalent iron was obtained in the earlier investigation but complexes with the $FeCl_4^-$ ion can be isolated. Tervalent chromium also forms sexi-covalent anionic complexes similar to those of ruthenium. The bromo- and chloro-complexes were precipitated as fine emerald-green and bluish-green crystals respectively. The analyses agreed with the empirical formula $Ru_2(Diarsine)_3X_6$; the possible

*Conductivities and magnetic moments of ruthenium complexes.*

| Compound * | Colour | Conductivity in $PhNO_2$: $\Lambda_M$ at 25° | Concn. ($10^{-3}$M) | $\chi_g \times 10^{-6}$ at 20·0° | $\chi_M \times 10^{-6}$ | Diamag. corrn. | $\chi_M' \times 10^{-6}$ | $\mu$ (B.M. per Ru atom) |
|---|---|---|---|---|---|---|---|---|
| $RuD_2Cl_2$ | Pale yellow | 0·4 | 0·33 | −0·13 | − 98 | 428 | — | 0·0 † |
| $RuD_2Br_2$ | Yellow-orange | 0·6 | 0·38 | −0·19 | −161 | 447 | — | 0·0 † |
| $RuD_2I_2$ | Orange | 0·6 | 0·28 | −0·16 | −150 | 467 | — | 0·0 † |
| $RuD_2I_2$ | Purple | 0·8 | 0·28 | −0·18 | −175 | 467 | — | 0·0 † |
| $RuD_2(CNS)_2$ | Silver-grey | 1·1 | 0·4 | −0·12 | − 97 | 439 | — | 0·0 † |
| $[RuD_2Cl_2]Cl$ | Green | 27·3 | 1·54 | 1·26 | 981 | 449 | 1430 | 1·83 |
| $[RuD_2Cl_2]ClO_4$ | Green | 29·4 | 0·50 | 1·29 | 1088 | 456 | 1544 | 1·91 |
| $[RuD_2Cl_2][RuDCl_4]$ | Blue-green | 34·9 | 2·1 | 1·75 | 2230 | 699 | 2929 | 1·86 |
| $[RuD_2Br_2]Br$ | Green | 26·0 | 0·54 | 1·23 | 1114 | 482 | 1596 | 1·94 |
| $[RuD_2Br_2][RuDBr_4]$ | Green | 35·4 | 1·7 | 1·67 | 2570 | 762 | 3332 | 1·97 |
| $[RuD_2I_2]ClO_4$ | Dark green | 27·2 | 1·0 | 1·01 | 1038 | 497 | 1535 | 1·90 |
| $[RuDCl_4]^-$ | — | — | — | — | 1249 | 273 | 1522 | 1·89 |
| $[RuDBr_4]^-$ | — | — | — | — | 1456 | 315 | 1771 | 2·04 |

* D = *o*-Phenylenebisdimethylarsine.

† These moments are regarded as formally zero. The small net paramagnetism after diamagnetic correction is attributed to small amounts of impurity and/or Van Vleck paramagnetism.

alternative formulation as $[Ru(Diarsine)_3][RuX_6]$ is unlikely for the following reasons. (1) The conductivities in nitrobenzene indicate that the complexes are uni-univalent electrolytes. (2) The $[RuX_6]^{3-}$ ion is orange-red, but the complexes isolated are green. Even if the $[Ru(Diarsine)_3]^{3+}$ ion were highly coloured, it is unlikely that the complex would be green if the red $[RuCl_6]^{3-}$ anion were present. (3) No other simple complexes of the $[Ru(Diarsine)_3]^{3+}$ could be prepared. These tervalent ruthenium complexes of the diarsine are very soluble in acetone or ethanol, but are rapidly reduced at the boiling point in these solvents. Reduction is slow at room temperature, however.

The addition of a slight excess of chlorine or bromine (X) to the bivalent ruthenium complex of iodine, $Ru(Diarsine)_2I_2$, results first in the formation of $[Ru(Diarsine)_2I_2]X$, then decomposition occurs forming $[Ru(Diarsine)_2X_2][Ru(Diarsine)X_4]$, iodine in the cation being oxidised to the free element. Iodine cannot be used as the oxidant because its oxidation potential is not high enough. Reduction of the tervalent ruthenium complexes can also be effected with iodide ion or sulphites, as well as with solvents like

acetone and alcohol. The perchlorates of the ruthenium(III) cation $[Ru(Diarsine)_2X_2]^+$ are difficult to obtain once the $[Ru(Diarsine)X_4]^-$ ion concentration becomes appreciable owing to the fact that the perchlorate is the more soluble salt. They may be formed if excess of perchloric acid in ethanol is added to the solutions of the bivalent complexes in chloroform before treatment with the oxidising agent (chlorine or bromine).

Potentiometric titrations with silver nitrate were carried out with the chloride $[Ru(Diarsine)_2Cl_2]Cl$ and with the bromide $[Ru(Diarsine)_2Br_2]Br$. The potentiometric end-points agreed well with the calculated titres for one-third of the total halogen in both cases, thus indicating that only one halogen atom is ionised. Conductivity measurements of the tervalent ruthenium complexes in nitrobenzene gave molecular conductivities between 26 and 35 mhos. The higher figures were obtained when the anion was $[RuDiarsineX_4]^-$, presumably owing to some dissociation of the anion. This effect was also observed with the $Cr^{III}$ complexes. This dissociation is also indicated by the unduly low molecular weight of the $[Ru(Diarsine)_2X_2][Ru(Diarsine)X_4]$ complexes in nitrobenzene solution. The conductivities of the ruthenium(III) complexes agree well with the figures for other uni-univalent electrolytes. Measurements of magnetic susceptibility gave magnetic moments of approximately 1·9 B.M. (see Table) for the rutherium(III) complexes, indicating one unpaired electron.

All attempts to obtain tris-diarsine complexes of ruthenium were unsuccessful. Prolonged refluxing of excess of diarsine with ruthenium halides in ethanol yielded complexes containing two molecules only of the ligand to each ruthenium atom. Attempts to prepare a tris-complex using ruthenium(III) perchlorate were also not successful. The colourless solution was refluxed with diarsine in ethanol for several hours, but all of the diarsine could be recovered. This reluctance of most tervalent metals to form tris-diarsine complexes has been referred to previously. Tri-oxalato- and tri-glycine complexes of ruthenium(III) were also treated unsuccessfully with the diarsine in attempts to prepare the required tris-diarsine complex. Repeated attempts to prepare ruthenium(IV) complexes were not successful. The use of 15N-nitric acid as oxidant, which yields $Fe^{IV}$, $Ni^{IV}$, and $Os^{IV}$ complexes, resulted in decomposition. As will be described in the next paper, stable osmium(IV) complexes can be obtained by this procedure. The failure to isolate ruthenium(IV) complexes similar to the iron(IV) compounds probably arises from their reactivity, since the quadrivalent state of ruthenium is well known in many complexes such as $K_2RuCl_6$ of which the iron analogues cannot be prepared.

## Experimental

*Dichlorodi-(o-phenylenebisdimethylarsine)ruthenium*(II).—Ruthenium(III) chloride (0·6 g.) in water (15 ml.) was added to *o*-phenylenebisdimethylarsine (1·2 g.) in purified ethanol (150 ml.) to give one phase. No reaction appeared to take place in the cold and the solution was heated under reflux for a few minutes. The pale yellow crystalline precipitate (0·6 g.) which formed was allowed to settle, separated by centrifuging, washed with cold ethanol, and dried *in vacuo*. A second crop of crystals was obtained by adding water, in which the complex is insoluble, to the mother-liquors. The use of hypophosphorous acid to assist in the reduction gave no greater yield (Found: C, 32·0; H, 4·2; Cl, 9·5%; *M*, ebullioscopic in 1·54% solution in chloroform, 680. $C_{20}H_{32}Cl_2As_4Ru$ requires C, 32·2; H, 4·3; Cl, 9·5%; *M*, 745). The *compound*, which is stable to above 360°, is soluble in chloroform and slightly soluble in warm ethanol, in which pale yellow solutions are obtained. It is also slightly soluble in methanol, acetone, nitrobenzene, and 1 : 4-dioxan, but insoluble in benzene, ether, and water. The compound is stable when freely exposed to air or water at room temperature. In dilute ethanol, silver nitrate gave only a slight turbidity when cold, but decomposition occurred on boiling, yielding a copious precipitate of silver chloride.

*Dibromodi-(o-phenylenebisdimethylarsine)ruthenium*(II).—Ruthenium(III) chloride (0·6 g.) in water (15 ml.) was treated with sodium bromide (1·5 g.), followed by diarsine (1·2 g.) in ethanol (150 ml.), filtered and brought to boiling as before. The subsequent treatment was the same as

that for the chloride. Orange-pink acicular crystals of the *bromide* (0·66 g.) were obtained and recrystallised from ethanol. As before, dilution with water gave a further crop of crystals (Found: C, 29·3; H, 4·0; Br, 19·5%; *M*, ebullioscopic in 1·14% solution in chloroform, 836. $C_{20}H_{32}Br_2As_4Ru$ requires C, 28·8; H, 3·8; Br, 19·2%; *M*, 834). The compound dissolves, but to a smaller extent, in the same solvents as the chloride. It was stable on heating to above 360°.

*Di-iodo-(o-phenylenebisdimethylarsine)ruthenium*(II).—*Orange form.* Ruthenium(III) chloride (0·6 g.) in water (15 ml.) was treated with sodium iodide (1·5 g.) and diarsine (1·2 g.) in ethanol (150 ml.), and the solution heated to boiling as before. The orange crystalline precipitate was allowed to settle before being separated by centrifuging. Owing to its low solubility in warm ethanol recrystallisation was not possible, but purification was effected by washing with water to remove alkali halide and ethanol, and then with ether to remove traces of diarsine. The *complex* was sparingly soluble in chloroform, dioxan, and nitrobenzene, and virtually insoluble in other common organic solvents. The practically quantitative yield (0·9 g.) may be attributed to the low solubility in ethanol (Found: C, 25·9; H, 3·5; I, 27·3; Ru, 11·4%; *M*, ebullioscopic in 1·24% solution in chloroform, 870. $C_{20}H_{32}I_2As_4Ru$ requires C, 25·9; H, 3·51; I, 27·4; Ru, 11·0%; *M*, 928).

*Purple form.* Ruthenium(III) chloride (0·6 g.) in water (10 ml.) was treated with sodium iodide (3·0 g.) and diarsine (1·2 g.) in ethanol (30 ml.), and the solution filtered and heated under reflux as above. The purple crystalline precipitate settled rapidly, and was separated as above. Purification was effected by washing consecutively with water, ethanol, and ether. Solutions in chloroform or nitrobenzene, in which the substance is sparingly soluble, were pale yellow, and the orange form was precipitated therefrom by concentration (Found: C, 25·95; H, 3·3; I, 27·8%). Molecular-weight determinations were not carried out because isomerism to the orange form took place in dilute solutions. On heating the compound is transformed into the orange form at about 370°.

*Dithiocyanatodi-(o-phenylenebisdimethylarsine)ruthenium*(II).—Ruthenium(III) chloride (0·25 g.) in water (6 ml.) was treated with ammonium thiocyanate (0·18 g.) and diarsine (0·65 g.) in ethanol (80 ml.), heated under reflux for 1 min., and set aside. The product which settled rapidly was removed by decantation and centrifuging. Recrystallisation from ethanol (250 ml.) gave silvery-grey crystals (0·33 g.), which were slightly soluble in chloroform, but only very sparingly soluble in dioxan and insoluble in benzene (Found: C, 33·3; H, 4·1; N, 3·2%; *M*, cryoscopic in 1·4% solution in nitrobenzene, 700. $C_{22}H_{32}N_2S_2As_4Ru$ requires C, 33·5; H, 4·1; N, 3·5%; *M*, 790).

*Dichlorodi-(o-phenylenebisdimethylarsine)ruthenium*(III) *Tetrachloromono-(o-phenylenebisdimethylarsine)ruthenate*(III).—The ruthenium(III) complexes were prepared from the corresponding ruthenium(II) compounds. The chloro-complex $[Ru(Diarsine)_2Cl_2]^0$ (0·45 g.) was dissolved in " AnalaR " chloroform (60 ml.) to a yellow solution and treated with a steady stream of dry chlorine for 10 min. at room temperature. The blue-green solution was concentrated by boiling off most of the chloroform, and precipitation of the complex assisted by the addition of a few drops of light petroleum. The *complex* (0·38 g.) was separated by centrifuging, washed once with chloroform, and dried in a vacuum. The bluish-green crystals are soluble in ethanol and acetone, reduction to the bivalent complex $[Ru(Diarsine)_2Cl_2]^0$ taking place in these solvents, slowly in cold solutions, but rapidly at the b. p. The filtrate remains reddish presumably owing to the presence of $Ru^{III}$ from the anion (Found: C, 28·2; H, 3·8; Cl, 16·7%; *M*, cryoscopic in 0·27% solution in nitrobenzene, 493. $C_{30}H_{48}Cl_6As_6Ru_2$ requires C, 28·3; H, 3·8; Cl, 16·7%; *M*, 1275). The compound decomposes at 233°.

*Dichlorodi-(o-phenylenebisdimethylarsine)ruthenium*(III) *Chloride.*—The complex $[Ru(Diarsine)_2Cl_2]^0$ (0·25 g.) in chloroform was treated simultaneously with dry hydrogen chloride and excess of dry chlorine, both as gas, the yellow solution becoming green. The chlorine was then stopped, and hydrogen chloride passed for a few more minutes; the mixture was then stirred and set aside. The green precipitate which formed was separated by centrifuging, washed with chloroform, then with a little alcohol and then several times with water and dried in vacuum (Found: C, 30·1; H, 3·9; Cl, 13·4%; *M*, cryoscopic in 0·68% solution in nitrobenzene, 360. $C_{20}H_{32}Cl_2As_4Ru$ requires C, 30·8; H, 4·1; Cl, 13·6%; *M*, 780). On heating, the compound decomposed near 200°. On warming with alcohol it was reduced to the $Ru^{II}$ complex $[RuCl_2(Diarsine)_2]^0$.

A potentiometric titration was carried out to determine the proportion of free chloride ion. $[Ru(Diarsine)_2Cl_2]Cl$ (0·0176 g.) in ethanol (15 ml.) was treated with acetone (35 ml.) and barium

nitrate (0·5 g.), and the solution titrated fairly rapidly with 0·00995N-silver nitrate with constant stirring. A sharp end-point after only 1 equiv. of silver ion had been added confirmed that only one Cl atom is ionised.

*Dichlorodi-(o-phenylenebisdimethylarsine)ruthenium*(III) *Perchlorate.*—The bivalent complex $[Ru(Diarsine)_2Cl_2]^0$ (0·15 g.) was dissolved in warm chloroform (25 ml.), and the solution filtered and treated with 70% perchloric acid (0·1 ml.) with sufficient ethanol to give one phase. Dry chlorine was bubled into the solution until a precipitate had commenced to form, whereupon passage of the chlorine was stopped and the mixture shaken with a few drops of light petroleum. As with the preparation of the chloride, excess of chlorine had to be avoided and the perchlorate anion introduced in excess before oxidation, because the salt containing the complex $[Ru(DiarsineCl_4]^-$ tends to be precipitated owing to lower solubility. The rest of the procedure was the same as that already described for the other tervalent ruthenium(III) complexes (Found: C, 28·6; H, 4·2; Ru, 11·8%; *M*, cryoscopic in 0·81% solution in nitrobenzene, 360. $C_{20}H_{32}O_4Cl_3As_4Ru$ requires C, 28·4; H, 3·8; Ru, 12·1%; *M*, 844); m. p. 265° (decomp.).

*Dibromodi-(o-phenylenebisdimethylarsine)ruthenium*(III) *Tetrabromomono-(o-phenylenebisdimethylarsine)ruthenate*(III).—The ruthenium(II) complex $[Ru(Diarsine)_2Br_2]^0$ (0·35 g.) was dissolved in chloroform (75 ml.), and bromine added in slight excess. The resulting deep green solution was evaporated to 25 ml., and the bright green crystals which were formed on shaking with a little light petroleum were separated by centrifuging, washed with chloroform, and dried ($H_2SO_4$) in a vacuum (0·30 g.). The complex gave bright green solutions in ethanol or acetone, but was reduced in these solvents by warming or on standing to the yellow $[Ru(Diarsine)_2Br_2]^0$, the solution remaining reddish owing to the presence of some ruthenium(III) bromide co-ordinated with solvent (Found: C, 23·4; H, 3·2%; *M*, cryoscopic in 0·26% solution in nitrobenzene, 650. $C_{30}H_{48}Br_6As_6Ru_2$ requires C, 23·4; H, 3·1%; *M*, 1542). The *salt* decomposed at 258°.

*Dibromodi-(o-phenylenebisdimethylarsine)ruthenium*(III) *Bromide.*—The ruthenium(II) complex $[Ru(Diarsine)_2Br_2]^0$ (0·3 g.) was dissolved in chloroform (50 ml.), the solution filtered, and hydrogen bromide and bromine passed through it for a few minutes. Excess of bromine was avoided to prevent development of a high concentration of $[Ru(Diarsine)Br_4]^-$ ion. Evaporation of the solution to about 20 ml. and addition of a few drops of light petroleum gave green crystals on agitation. The latter were separated by centrifuging, washed with chloroform and water, and dried in a vacuum. The *bromide* is soluble in ethanol and acetone but, like the corresponding chloro-complex, is reduced by these reagents in hot solution (Found: C, 26·0; H, 3·4; Br, 26·4%; *M*, cryoscopic in 0·31% solution in nitrobenzene, 420. $C_{20}H_{32}Br_2As_4Ru$ requires C, 26·3; H, 3·5; Br, 26·3%; *M*, 913); m. p. 230° (decomp.). A potentiometric titration in ethanol–acetone indicated that only one Br atom was ionised.

*Di-iododi-(o-phenylenebisdimethylarsine)ruthenium*(III) *Perchlorate.*—The ruthenium(III) complex $[Ru(Diarsine)_2I_2]^0$ (0·2 g.) in warm chloroform (50 ml.) was treated with perchloric acid (0·1 g.) in ethanol (5 ml.) and the calculated proportion of bromine (0·018 g.) was added. The solution, which became deep green, was evaporated to 30 ml., and the sage-green crystals which formed were separated by centrifuging as before. After being washed with chloroform, these (0·14 g.) were dried in a vacuum (Found: C, 22·8; H, 3·0; Ru, 10·1%; *M*, cryoscopic in 1·0% solution in nitrobenzene, 480. $C_{20}H_{32}O_4ClI_2As_4Ru$ requires C, 23·4; H, 3·1; Ru, 9·9%; *M*, 1028). Addition of sodium iodide to an alcoholic solution of the *complex* caused liberation of free iodine, with immediate reduction to the bivalent complex $[Ru(Diarsine)_2I_2]^0$. Treatment of the latter with excess of bromine in the absence of perchlorate anion gave the bromo-complex $[Ru(Diarsine)_2Br_2][RuDiarsineBr_4]$. The complex $[RuDiarsineI_4]^-$ anion was not obtained (contrast the chromium complex).

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON.
SCHOOL OF APPLIED CHEMISTRY (GRANVILLE COLLEGE),
N.S.W. UNIVERSITY OF TECHNOLOGY, SYDNEY AUSTRALIA. [*Received, August 7th*, 1957.]

XUM

## 111. *Studies in Co-ordination Chemistry. Part XVIII.* Complexes of Osmium with a Di(tertiary Arsine).*

By R. S. Nyholm and G. J. Sutton.

Complexes of bivalent, tervalent, and quadrivalent osmium halides with the di(tertiary arsine) chelate group *o*-phenylenebisdimethylarsine have been prepared and studied. The bivalent osmium complexes are diamagnetic, sexicovalent non-electrolytes of the type $[Os(Diarsine)_2X_2]^0$ and are similar to the compounds formed by iron(II) and ruthenium(II). Oxidation of these osmium(II) complexes with halogens yields osmium(III) salts of the type $[Os(Diarsine)_2X_2]X$. The magnetic moments of these are in the range 1·7—2·0 B.M., indicating one unpaired electron. Treatment of these osmium(III) compounds with concentrated nitric acid yields, as with nickel and iron, quadrivalent osmium compounds. The magnetic moments of the osmium(IV) derivatives are only about 1·2 B.M., as observed previously for compounds such as $K_2OsCl_6$. Electrical-conductivity and molecular-weight measurements where possible have been carried out.

In this paper we complete the discussion of the complexes of the Fe, Ru, Os triad by describing the compounds of osmium. Some earlier work [1] with dimethylphenyl- and methyldiphenyl-arsine led to the isolation of complexes of the types $[Os^{II}X_2,4AsR_3]^0$ and $[Os^{III}X_3,3AsR_3]^0$ but the magnetic properties were not investigated. No compounds of osmium(IV) were described. As with ruthenium, the investigation of the di(tertiary arsine) complexes of osmium was initiated partly in order to attempt to stabilise less common valency states but also to compare the magnetic properties of the complexes of the various valency states with those of the other transition metals. Special interest attaches to osmium(IV) complexes because they usually have moments even less than those corresponding with the two spins expected on Pauling's theory; thus the moment of $K_2OsCl_6$ is only 1·4 B.M. at room temperatures.

*Bivalent Osmium Compounds.*—These were prepared simply by treating the osmium(IV) hexahalide anions with excess of di(tertiary arsine) in alcohol. Reduction to the tervalent state first took place, but further heating yielded the insoluble osmium(II) compounds. The chloride, bromide, iodide, and thiocyanate were prepared, and their properties are given in the Table. They are diamagnetic and non-electrolytes in nitrobenzene, in which solvent they are also monomeric. No evidence for two forms of the iodide as observed with ruthenium was obtained. The two halogen atoms are probably *trans*, but *X*-ray investigations are needed to determine this.

*Tervalent Osmium Compounds.*—These were conveniently prepared by oxidising the corresponding osmium(II) compounds with the appropriate halogen. They are all salt-like compounds having the general formula $[Os(Diarsine)_2X_2]X$. The molecular-weight measurements in nitrobenzene show that they are highly dissociated, and the molecular conductivities show that they are uni-univalent electrolytes in this solvent. Magnetic susceptibilities indicate the presence of one unpaired electron, as expected for the tervalent state. It may also be shown by potentiometric titration of the chloride ion that only one of the three halogen atoms in the compound $[Os(Diarsine)_2Cl_2]Cl$ is ionised. The properties of the tervalent complexes are summarised in the Table.

*Quadrivalent Osmium Compounds.*—Compounds of tervalent nickel of the type $[NiCl_2(Diarsine)_2]Cl$ and the corresponding iron(III) cation can be oxidised by 15N-nitric acid to yield compounds in which the metal is quadrivalent. This method has now been applied to obtain osmium(IV) di(tertiary arsine) complexes after it had been found that commoner oxidising agents such as the permanganate and cerate ions in water failed to achieve this. Compounds of the type $[Os^{IV}X_2(Diarsine)_2][ClO_4]_2$ (where X = Cl, Br, I)

* Part XVII, preceding paper.

[1] Dwyer, Nyholm, and Tyson, *J. Proc. Roy. Soc. N.S.W.*, 1948, **81**, 272.

have been prepared and their properties investigated. In nitrobenzene solution they behave as bi-univalent electrolytes, but as they are only sparingly soluble in this solvent it was not possible to determine molecular weights. The magnetic moments expected for a $d_\epsilon^4$ configuration ($Os^{IV}$) on the basis of Hund's rule is 2·83 B.M. However, values much

*Properties of osmium–diarsine complexes.*

| | | Molecular conductivity in $PhNO_2$ at 25° | | Magnetic susceptibility at 20° | | | | |
|---|---|---|---|---|---|---|---|---|
| Compound * | Colour | $\Lambda_M$ | Concn. ($10^{-3}$M) | $\chi_g \times 10^{-6}$ | $\chi_M \times 10^{-6}$ | Diamag. corrn. | $\chi_M$ (corr.) $\times 10^{-6}$ | $\mu_{eff}$ (B.M.) |
| $[OsD_2Cl_2]$ ..... | Pale yellow | 0·7 | 1·33 | −0·22 | −184 | 426 | — | 0·0 † |
| $[OsD_2Br_2]$ ..... | Pale brown | 0·4 | 1·45 | −0·22 | −205 | 447 | — | 0·0 † |
| $[OsD_2I_2]$ ..... | Dark brown | 0·4 | 0·87 | −0·22 | −221 | 467 | — | 0·0 † |
| $[OsD_2(SCN)_2]$ ..... | Light brown | 1·3 | 0·40 | −0·20 | −176 | 439 | — | 0·0 † |
| $[OsD_2Cl_2]Cl$ ..... | Purple-red | 21·4 | 1·62 | 1·136 | 985 | 449 | 1434 | 1·85 |
| $[OsD_2Cl_2]ClO_4$ ..... | Purple-red | 22·7 | 0·86 | 1·07 | 998 | 456 | 1454 | 1·86 |
| $[OsD_2Br_2]Br$ ..... | Purple-blue | 21·8 | 2·0 | 1·02 | 1022 | 482 | 1504 | 1·88 |
| $[OsD_2Br_2]ClO_4$ ..... | Purple-blue | 23·3 | 1·18 | 1·04 | 1063 | 477 | 1540 | 1·91 |
| $[OsD_2I_2]Br$ ..... | Blue-green | 25·8 | 0·35 | 1·00 | 1096 | 502 | 1598 | 1·93 |
| $[OsD_2I_2]ClO_4$ ..... | Blue-green | 23·2 | 1·18 | 0·99 | 1083 | 497 | 1580 | 1·93 |
| $[OsD_2(SCN)_2]ClO_4$ | Blue | 22·5 | 0·50 | 1·05 | 1027 | 469 | 1496 | 1·88 |
| $[OsD_2Cl_2][ClO_4]_2$ ... | Blue-black | 43·2 | 0·83 | 0·173 | 178 | 486 | 664 | 1·25 |
| $[OsD_2Br_2][ClO_4]_2$ ... | Black | 42·2 | 0·56 | 0·109 | 122 | 507 | 629 | 1·22 |
| $[OsD_2I_2][ClO_4]_2$ ... | Brown-black | 44·2 | 0·66 | 0·038 | 46 | 527 | 573 | 1·16 |

* D = *o*-Phenylenebisdimethylarsine.

† These moments are regarded as formally zero. The small net paramagnetism after making the diamagnetic correction is attributed to small amounts of impurity and/or Van Vleck paramagnetism.

less than this are observed; in these complexes values from 1·16 to 1·25 B.M. were obtained. Kotani [2] has explained this behaviour by examining the effect of the large nuclear charge of the $Os^{IV}$ atom upon the spin-orbit interaction, and concludes that as the temperature decreases the paramagnetism should steadily decrease, $\mu_{eff}$ being proportional to $\sqrt{T}$ at room temperature. This has been confirmed for $K_2OsCl_6$ by Johannsen and Lindberg [3] and for some other osmium(IV) complexes by Figgis and Nyholm.[4] A more detailed interpretation of the results on these and other osmium complexes will be presented in due course. For a more detailed discussion, see Earnshaw *et al.*[5]

Many attempts to prepare compounds containing a trisdiarsineosmium ion, *i.e.*, $[Os(Diarsine)_3]^{n+}$, were unsuccessful. As before, we attribute this to the reluctance of osmium to accept too large a negative charge.

## Experimental

*Dichlorodi-(o-phenylenebisdimethylarsine)osmium*(II).—Ammonium hexachloro-osmate (0·25 g.) in water (5 ml.) was added to ethanol (50 ml.) and diarsine (0·34 g.), one phase being obtained. The mixture was heated under reflux, and after a few minutes the colour changed from orange to cherry-red as the $[Os(Diarsine)_2Cl_2]^+$ ion was formed. After a further ½ hr. the colour had

[2] Kotani, *J. Phys. Soc. Japan*, 1949, **4**, 293.
[3] Johannsen and Lindberg, *J. Amer. Chem. Soc.*, 1954, **76**, 5349.
[4] Figgis, Thesis, N.S.W., 1955.
[5] Earnshaw, Figgis, Lewis, and Nyholm, *Nature*, 1957, **179**, 1121.

become pale orange. The heating was stopped after another ½ hr., the reduction being complete. On standing, a pale yellow precipitate settled out. The latter (0·16 g.) was separated by centrifuging, washed with ethanol, and dried in a vacuum. The *complex* is oxidised readily by permanganate, dichromate, chlorine or bromine when suspended in ethanol, acetone, or dioxan. It was stable to above 360° (Found: Cl, 8·30; Os, 22·5%; *M*, cryoscopic in 0·12% solution in nitrobenzene, 750. $C_{20}H_{32}Cl_2As_4Os$ requires Cl, 8·5; Os, 22·8%; *M*, 833). Potentiometric titration of this compound in acetone solution with dichromate and use of a platinum electrode showed that $E_0$ for oxidation to the osmium(III) complex is approx. 0·6—0·7 v.

*Dibromodi-*(o-*phenylenebisdimethylarsine*)*osmium*(II).—Ammonium hexabromo-osmate(IV) (0·36 g.), together with diarsine (0·28 g.) and ethanol to form one phase, were heated under reflux as above. Reduction first produced in solution the purple blue $[Os(Diarsine)_2Br_2]^+$ ion, but heating was continued until a brownish-pink colour had developed. A further ½ hr. was allowed to ensure completion of reduction, and separation of the fawn-brown crystalline solid (0·2 g.) was carried out as for the chloride. When heated, the *compound* did not decompose below 360° (Found: Br, 17·1; Os, 20·4%; *M*, cryoscopic in 0·14% solution in nitrobenzene, 820. $C_{20}H_{32}Br_2As_4Os$ requires Br, 17·35; Os, 20·6%; *M*, 922).

*Di-iododi-*(o-*phenylenebisdimethylarsine*)*osmium*(II).—Ammonium hexabromo-osmate(IV) (0·42 g.) and sodium iodide (2 g.) in water together with diarsine (0·3 g.) were refluxed in sufficient ethanol as before. The reaction was carried beyond the bluish stage, $[Os(Diarsine)_2I_2]^+$ formation, until a light cinnamon-brown precipitate had formed, and then continued for a further ½ hr. The fine crystalline solid (0·25 g.) which separated was washed free from impurities and dried as before. Owing to extremely low solubility in suitable solvents, recrystallisation was not practicable. The *complex* is very slightly soluble in methanol, giving a pale yellow solution; it did not decompose below 360°. Molecular-weight determinations were not possible owing to the low solubility in all solvents (Found: I, 24·4; Os, 18·5. $C_{20}H_{32}I_2As_4Os$ requires I, 25·0; Os, 18·7%).

*Dithiocyanatodi-*(o-*phenylenebisdimethylarsine*)*osmium*(II).—Ammonium hexabromo-osmate-(IV) (0·9 g.), together with ammonium thiocyanate (3 g.) in water (5 ml.) and diarsine (0·75 g.), was refluxed in ethanol (50 ml.). The original orange colour changed to bluish-green after 15 min. and to a dull yellow after 1 hr. On standing, a light brown, powdery precipitate settled out. The complex (0·4 g.) was washed, and dried in a vacuum as already described. The substance is soluble in methanol, but almost insoluble in other common organic solvents. Like the corresponding halides, the *complex* did not decompose below 360°. Molecular-weight determination was not possible owing to the low solubility in nitrobenzene (Found: CNS, 13·1; Os, 21·3. $C_{22}H_{32}N_2S_2As_4Os$ requires CNS, 13·22; Os, 21·6%).

*Dichlorodi-*(o-*phenylenebisdimethylarsine*)*osmium*(III) *Chloride*.—The osmium(II) complex $[Os(Diarsine)_2Cl_2]^0$ (0·1 g.) was suspended in methanol (150 ml.) at 40°, and chlorine bubbled through until there was no solid left in suspension, the solution becoming red. After filtering, a saturated solution of calcium chloride in ethanol (10 ml.) was added, followed by 25 ml. of water. Red monoclinic crystals of the tervalent osmium *complex* were precipitated. These were removed by centrifuging, washed with a little dilute ethanol to remove calcium chloride, and dried in a vacuum. The substance was recrystallised from acetone–1 : 4-dioxan. The red crystals decomposed at 255° (Found: Cl, 12·3; Os, 21·9%; *M*, in 0·13% solution in nitrobenzene, 360. $C_{20}H_{32}Cl_3As_4Os$ requires Cl, 12·3; Os, 21·9%; *M*, 868). As a check on the valency state of the osmium, a solution of the complex was treated with aqueous potassium iodide, and the liberated iodine titrated with 0·1N-sodium thiosulphate solution. The titre agreed closely with the calculated volume for the liberation of 1 equiv. of iodine.

*Dichlorodi-*(o-*phenylenebisdimethylarsine*)*osmium*(III) *Perchlorate*.—The chloride complex of bivalent osmium $[Os(Diarsine)_2Cl_2]^0$ (0·078 g.) was suspended in methanol (50 ml.) and chlorine passed through until all the complex had dissolved to form the red solution of the tervalent complex. After filtering, the solution was treated with perchloric acid (1 ml.) and evaporated carefully to about half its bulk; no precipitate was formed until water (15 ml.) was added; red powdery crystals of the *perchlorate* then settled out. The complex (0·07 g.) was separated and dried as for the corresponding chloride. The substance was soluble in methanol and dioxan–acetone, slightly soluble in ethanol and in acetone, very sparingly soluble in dioxan, and insoluble in chloroform, carbon tetrachloride, benzene, toluene, ether, and water. It decomposed explosively at 293° (Found: Cl, 12·0; Os, 20·4%; *M*, in 0·11% solution in nitrobenzene,

440. $C_{20}H_{32}O_4Cl_2As_4Os$ requires Cl, 11·4; Os, 20·4%; *M*, 933). Potentiometric titration with silver nitrate in acetone solution and use of a silver electrode established that only one chlorine atom is ionised.

*Dibromodi-(o-phenylenebisdimethylarsine)osmium*(III) *Bromide*.—The bivalent osmium complex (0·1 g.) was oxidised by bromine in methanol (100 ml.) at 40°. The bromine was added in alcoholic solution, excess being avoided. The purple solution which formed was filtered, and a solution of sodium bromide (0·2 g.) in methanol (5 ml.) added. On standing, purple-blue crystals (0·15 g.) of the tervalent *complex* were obtained. It decomposed at 304°, and was slightly soluble in ethanol, sparingly soluble in acetone and dioxan, and almost insoluble in benzene, carbon tetrachloride, chloroform, and ether. However, the substance dissolved very readily in dioxan–acetone (1 : 1) (Found: Br, 24·7; Os, 18·75%; *M*, cryoscopic in 0·12% solution in nitrobenzene, 506. $C_{20}H_{32}Br_2As_4Os$ requires Br, 24·0; Os, 18·96%; *M*, 1002). Potentiometric titration with silver nitrate in acetone solution with a silver electrode showed that only one bromine atom is ionised.

*Dibromodi-(o-phenylenebisdimethylarsine)osmium*(III) *Perchlorate*.—An alternative method of preparation directly from the hexabromo-osmate ion was used. To $(NH_4)_2OsBr_6$ (0·369 g.) in water (5 ml.), diarsine (0·3 g.) was added, and a homogeneous phase obtained by addition of ethanol. The solution was heated under reflux until a violet-blue colour had developed, and was then filtered, and perchloric acid (1 ml.) added to the filtrate. On standing, purple-blue crystals (0·21 g.) of the required *complex* settled out. These were washed with alcoholic ether to remove any diarsine and recrystallised from acetone–dioxan, in a vacuum. The complex decomposed at 302° with explosive violence (Found: Os, 18·8%; *M*, in 0·2% solution in nitrobenzene, 470. $C_{20}H_{32}O_4Br_2ClAs_4Os$ requires Os, 18·6%; *M*, 1022).

*Di-iododi-(o-phenylenebisdimethylarsine)osmium*(III) *Bromide*.—The osmium complex $[Os(Diarsine)_2I_2]^0$ (0·1 g.) was suspended in methanol (100 ml.), and the calculated proportion of bromine in methanol added cautiously with stirring. The solution was then filtered, and water (25 ml.) added. The blue-green precipitate (0·1 g.) which formed was separated by decantation and centrifuging, washed with dilute ethanol, and dried ($H_2SO_4$) in a vacuum-desiccator. The *complex* is soluble in acetone–dioxan to a bluish-green solution. On heating it decomposed at 288°. Owing to its low solubility in nitrobenzene its molecular weight was not measured (Found: Os, 17·3. $C_{20}H_{32}BrI_2As_4Os$ requires Os, 17·35%).

*Di-iododi-(o-phenylenebisdimethylarsine)osmium*(III) *Perchlorate*.—Ammonium hexabromo-osmate (0·36 g.), sodium iodide (0·16 g.), diarsine (0·25 g.), and ethanol (50 ml.) were refluxed together until a greyish-blue colour had developed. The mixture was then filtered, and the filtrate treated with perchloric acid (3 ml.). The green precipitate (0·15 g.) which formed was filtered and purified by recrystallisation from acetone–dioxan and dried in vacuum. The *perchlorate* decomposes on heating at 273° (Found: Os, 17·1%; *M*, in 0·1% solution in nitrobenzene 500. $C_{20}H_{32}O_4ClI_2As_4Os$ requires Os, 17·1%; *M*, 1115).

*Dithiocyanatodi-(o-phenylenebisdimethylarsine)osmium*(III) *Perchlorate*.—Ammonium hexabromo-osmate(IV) (0·31 g.), ammonium thiocyanate (0·4 g.), diarsine (0·23 g.), and ethanol 95% (50 ml.) were refluxed together until a light blue colour had developed, then filtered; perchloric acid (2 ml.) was added, and the solution evaporated to 25 ml. on a water-bath. Addition of water (25 ml.) yielded a precipitate of the *perchlorate* (0·16 g.). This was removed by centrifuging, washed with ether, and reprecipitated from acetone–dioxan. It decomposed with explosive violence at 265° (Found: Os, 19·2%; *M*, cryoscopic in 0·10% solution in nitrobenzene, 450. $C_{22}H_{32}O_4N_2ClS_2As_4Os$ requires Os, 19·4%; *M*, 977).

*Dichlorodi-(o-phenylenebisdimethylarsine)osmium*(IV) *Perchlorate*.—The red tervalent osmium complex $[Os(Diarsine)_2Cl_2]Cl$ (0·1 g.) was treated with 15N-nitric acid (3 ml.) with stirring until all had dissolved. A few drops of perchloric acid were then added to the green solution, and the mixture left in a refrigerator. After several hours, the blue-black crystals which had settled out were separated by centrifuging, shaken rapidly with three portions of cold anhydrous ether to remove any nitric or perchloric acids and any traces of products of oxidation, and dried in a vacuum [Found: Cl (total), 13·5; Os, 18·5. $C_{20}H_{32}O_8Cl_4As_4Os$ requires C, 13·75; Os, 18·5%]. When heated at 160° the *complex* decomposed, first turning red, the colour of the tervalent compound.

*Dibromodi-(o-phenylenebisdimethylarsine)osmium*(IV) *Perchlorate*.—The blue complex $[Os(Diarsine)_2Br_2]Br$ (0·1 g.) was treated with 15N-nitric acid as above, a green solution being formed. Addition of perchloric acid, and subsequent treatment as for the above chloro-complex, led to

black shiny crystals (0·11 g.) (Found: Os, 17·2. $C_{20}H_{32}O_8Br_2Cl_2As_4Os$ requires Os, 17·0%). When heated, the *perchlorate* decomposed at 194°.

*Di-iododi-(o-phenylenebisdimethylarsine)osmium*(IV) *Perchlorate*.—The green compound $[Os(Diarsine)_2I_2]ClO_4$ (0·04 g.) was oxidised with concentrated nitric acid as before, and after the addition of perchloric acid and cooling, dark brown crystals of the osmium(IV) *complex* (0·04 g.) were precipitated from the golden-yellow solution. The complex was then washed with cold anhydrous ether and dried in a vacuum (Found: Os, 15·7. $C_{20}H_{32}O_8Cl_2I_2As_4Os$ requires Os, 15·6%). The compound decomposed on heating to 210°.

*Potentiometric Titration: Oxidation–Reduction*.—The yellow complex $[Os(Diarsine)_2Cl_2]$ (0·1580 g.) was dissolved in acetone (80 ml.) together with 5N-sulphuric acid (80 ml.), and the homogeneous mixture titrated with 0·01N-potassium dichromate solution from a microburette. The reaction was carried out in a carbon dioxide atmosphere, a sharp end-point being obtained after adding 1 equiv. of oxidising agent. $E_0$ was estimated at 0·6—0·7 v.

The authors are grateful to Messrs. Garrett, Davidson, and Matthey, of Sydney, Australia, for the loan of the osmium and ruthenium used in the work reported in this and the preceding paper.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON.
SCHOOL OF APPLIED CHEMISTRY (GRANVILLE COLLEGE),
N.S.W. UNIVERSITY OF TECHNOLOGY, SYDNEY, AUSTRALIA. [*Received, August 7th*, 1957.]

---

## 112. *Rearrangements of Some* cyclo*Octatetraene Derivatives.*

By C. R. GANELLIN and R. PETTIT.

A mechanism which involves intermediate formation of *cyclo*hepta-2 : 4 : 6-trienealdehyde is postulated for the acid-catalysed rearrangement of 7 : 8-epoxy*cyclo*octa-1 : 3 : 5-triene to phenylacetaldehyde. The epoxide gives tropylium salts in poor yield when oxidised by acid permanganate; with 2 : 4-dinitrophenylhydrazine in acidic alcohol below 0° it gives mainly the hydrazone of *cyclo*hepta-2 : 4 : 6-trienealdehyde, but at 70° gives the hydrazone of phenylacetaldehyde. Rearrangement in acids of those *cyclo*heptatriene derivatives capable of giving rise to ions of the type (VIII), to benzene derivatives, appears to be a general reaction.

A similar mechanism accounts for other rearrangements of *cyclo*octatetraene derivatives. The dichloride of *cyclo*octatetraene with methanol gives phenylacetaldehyde dimethyl acetal, and not phenylglycol dimethyl ether as reported earlier.

*cyclo*OCTATETRAENE [1] and its derivatives undergo a variety of rearrangements, but so far there is little to indicate their mechanisms. In this paper we suggest a route for some of them, in particular the acid-catalysed rearrangement of 7 : 8-epoxy*cyclo*octa-1 : 3 : 5-triene (*cyclo*octatetraene oxide) to phenylacetaldehyde and the solvolytic reactions of *cyclo*octatetraene dichloride.

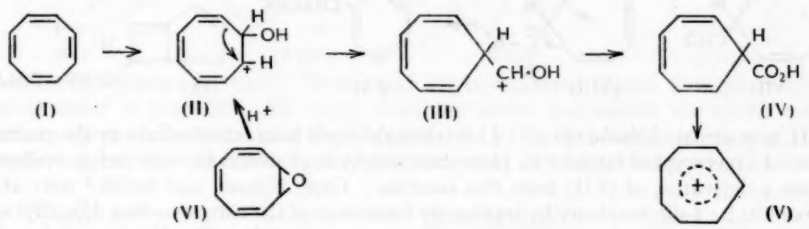
We recently reported [2] that the tropylium cation (V) was one of the products formed when *cyclo*octatetraene (I) was oxidised with acid potassium permanganate. We suggested initial formation of the hydroxy-cation (II), which gave the protonated *cyclo*hepta-2 : 4 : 6-trienealdehyde * (III) by a pinacol–pinacone rearrangement. Compound (III) was then supposed to be oxidised to *cyclo*hepta-2 : 4 : 6-trienecarboxylic acid (IV) which gives the tropylium cation on reaction [3] with oxidising agents.

Known reactions of epoxides with acids suggested that the cation (II) could be formed

* By analogy with the corresponding acid [3] the 2 : 4 : 6-*cyclo*heptatriene formulation is preferred to a norcaradiene structure for this aldehyde, and is used also for other such compounds in this paper.

[1] Reppe, Schlichting, Klager, and Toepel, *Annalen*, 1948, **560**, 1.
[2] Ganellin and Pettit, *J. Amer. Chem. Soc.*, 1957, **79**, 1767.
[3] Dewar, Ganellin, and Pettit, *J.*, 1957, 55.

by treating 7 : 8-epoxy*cyclo*octa-1 : 3 : 5-triene (VI) with acids:[4] thus oxidation with acid permanganate should yield the tropylium cation. We have obtained a 7% yield of tropylium picrate from this reaction. The low yield is not surprising, since the tropylium cation itself is readily destroyed by permanganate,[5] and is of the same order as that obtained by oxidation of *cyclo*octatetraene with acid permanganate.




*Acid-catalysed Rearrangement of* 7 : 8-*Epoxy*cyclo*octa*-1 : 3 : 5-*triene to Phenylacetaldehyde.*—In the above mechanism for the oxidation of the epoxide, the first step is the acid-catalysed rearrangement to the cation (III), and the oxidant does not enter into the reaction until this has taken place. This suggests that acid-catalysed rearrangement of the oxide to phenylacetaldehyde[1] may involve intermediate formation of the aldehyde (VII) which subsequently rearranges to phenylacetaldehyde. We have so far been unable to synthesise this aldehyde, but from the following similar reactions there can be little doubt that it would isomerise to phenylacetaldehyde in mineral acid.

The acid-catalysed rearrangement of *cyclo*hepta-1 : 3 : 5-triene derivatives which are capable of giving rise to ions of the type (VIII) appears to be general, the products being ββ′-disubstituted styrene derivatives having the general formula (IX), the driving force arising from the larger resonance energy developed in the aromatic ring.

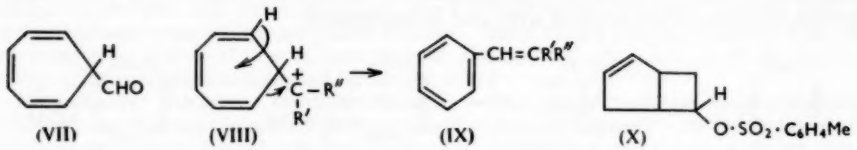
The rearrangement occurs when the cation (VIII) is produced by addition of a proton or by acid-catalysed removal of a hydroxyl group. Thus *cyclo*hepta-2 : 4 : 6-trienyl methyl ketone readily rearranges to benzyl methyl ketone in warm dilute alcoholic hydrochloric acid. This involves, first, the addition of a proton with formation of the cation (VIII; R′ = Me, R″ = OH), then rearrangement to (IX; R′ = Me, R″ = OH) which is the enolic form of benzyl methyl ketone. Similarly, 2-(*cyclo*hepta-2 : 4 : 6-trienyl)propan-2-ol (VIII; R′ = Me, R″ = Me) readily rearranges in dilute alcoholic hydrochloric acid to 2′-methylpropenylbenzene, and Doering[6] has found that *cyclo*hepta-2 : 4 : 6-trienylmethanol undergoes acid-catalysed rearrangement to styrene. It is interesting that the addition of phenylmagnesium bromide to 7-cyano*cyclo*hepta-1 : 3 : 5-triene, followed by hydrolysis with acid, gives deoxybenzoin and not *cyclo*heptatrienyl phenyl ketone:[7] this could occur by intermediate formation of the cation (VIII; R′ = Ph, R″ = OH).

Cope, Nelson, and Smith[8] prepared *cyclo*hepta-2 : 4 : 6-trienealdehyde dimethyl acetal from the dichloride of *cyclo*octatetraene and found that it yields phenylacetaldehyde on hydrolysis in aqueous acid. It is possible that the acetal is first hydrolysed to the aldehyde (VII) which then rearranges, *via* the ion (VIII; R′ = H, R″ = OH), to the enolic form of phenylacetaldehyde. Alternatively, rearrangement of the acetal can take place through the ion (VIII; R′ = H, R″ = OMe), to give β-methoxystyrene which undergoes acid hydrolysis very readily to phenylacetaldehyde.

In anhydrous methanol acid-catalysed rearrangement of the acetal should proceed *via* the ion (VIII; R′ = H, R″ = OMe), to give β-methoxystyrene. However, the product

[4] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1953, p. 344.
[5] Dewar and Pettit, *J.*, 1956, 2026.
[6] Professor W. von E. Doering, personal communication.
[7] Doering and Knox, *J. Amer. Chem. Soc.*, 1957, **79**, 352.
[8] Cope, Nelson, and Smith, *J. Amer. Chem. Soc.*, 1954, **76**, 1100.

we obtained was phenylacetaldehyde dimethyl acetal. This is understandable in view of our finding that β-methoxystyrene readily adds the elements of methanol under the conditions used in the rearrangement.




(VII) (VIII) (IX) (X)

If, as postulated, *cyclo*hepta-2 : 4 : 6-trienealdehyde is an intermediate in the rearrangement of epoxy*cyclo*octatriene to phenylacetaldehyde it would be convincing evidence to isolate a derivative of (VII) from this reaction. Cope, Nelson, and Smith [8] were able to prepare its 2 : 4-dinitrophenylhydrazone by treatment of the corresponding dimethyl acetal with 2 : 4-dinitrophenylhydrazine in acidic aqueous ethanol at 0°. We have isolated this 2 : 4-dinitrophenylhydrazone as the major product of the reaction of the epoxide with 2 : 4-dinitrophenylhydrazine in aqueous acidic ethanol at −5°. A similar reaction at 70° gave as main product the corresponding derivative of phenylacetaldehyde. Rearrangement of the intermediate aldehyde (VII) must be sufficiently slow at lower temperatures to allow formation of the hydrazone.

These results provide good evidence that a seven-membered ring intermediate is involved in the acid-catalysed rearrangement of epoxy*cyclo*octatriene to phenylacetaldehyde. The gain in resonance energy [9] and a decrease in the steric strain involved in going from the *cyclo*octatriene to the *cyclo*heptatriene system would provide the driving force for the initial ring-contraction. The same arguments could account for the production of *cyclo*heptatriene in 50% yield on acetolysis of the toluene-*p*-sulphonate [10] (X).

*Rearrangements of the Dichloride of* cyclo*Octatetraene.*—The products obtained from solvolytic reactions of the dichloride (XII; R = R′ = Cl) vary remarkably with the medium and may have one of three different ring systems. Hydrolysis in water produces phenylacetaldehyde. Reppe *et al.*[1] found that treatment with acetic acid gave β-acetoxystyrene, whereas that with potassium acetate in acetic acid gave the diacetoxy-compound (XII; R = R′ = OAc). Cope, Nelson, and Smith [8] have shown that the dichloride with sodium methoxide in methyl alcohol gives *cyclo*hepta-2 : 4 : 6-trienealdehyde dimethyl acetal, and not compound (XI) as reported by Reppe *et al.*[1] All these products are readily accounted for by a scheme similar to that described above for the rearrangement of the epoxide.

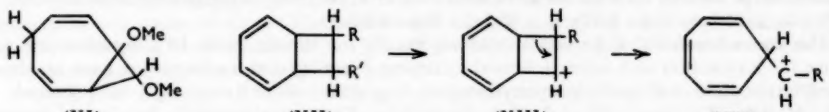
Hydrolysis of the dichloride in water would proceed *via* the cation * (XIII; R = OH); a pinacol–pinacolone rearrangement would then give protonated *cyclo*heptatrienealdehyde (VIII; R = OH), which, under the acid conditions produced by the hydrolysis, would rearrange to phenylacetaldehyde as described earlier. Similarly, solvolysis of the dichloride in the absence of base would occur with the production (in the presence of the hydrochloric acid liberated) of the cation (VIII; R = OAc) which would rearrange to β-acetoxystyrene. Acetolysis of the dichloride in acetic acid containing potassium acetate involves no rearrangement. Possibly this reaction involves $S_N2$ substitution by the acetate ion; no intermediate cation of the type (XIII) would then be formed. Methanolysis in the presence of base could proceed by rearrangement of the cation (XIII; R = OMe) to the cation (VIII; R = OMe), which would yield the dimethyl acetal of the

* There is good evidence that the dichloride has the bicyclic structure (XII), but in view of the ready conversion of the bicyclic system into the eight-membered ring shown by some compounds, *e.g.*, *cyclo*octatrienes, there can be no justification for preferring either the bicyclic or the monocyclic structure for the cations (XIII).

[9] Doering and Knox, *J. Amer. Chem. Soc.*, 1956, **78**, 5448.
[10] Dryden, *ibid.*, 1954, **76**, 2841.

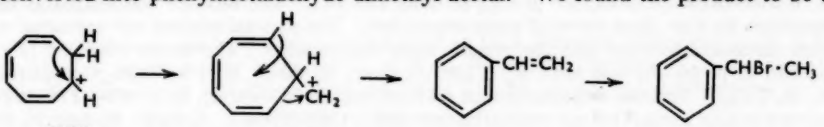
aldehyde (VII) by reaction with methoxide ion and, under the basic conditions prevailing, no further rearrangement would be expected.

We have re-investigated the products of methanolysis of the dichloride in methyl



(XI) (XII) (XIII) (VIII)

alcohol in the absence of base. Reppe and his co-workers [1] report that phenylglycol dimethyl ether is produced. However, from the above mechanism we would expect β-methoxystyrene to be formed, *via* the ions (XIII and VIII; R = OMe), which would then be converted into phenylacetaldehyde dimethyl acetal. We found the product to be this



(XIV) (XV)

acetal which, though similar in some respects to phenylglycol dimethyl ether, has a different infrared absorption spectrum. The two compounds can readily be distinguished by the much faster hydrolysis of the acetal to phenylacetaldehyde.

*Other Rearrangements.*—Willstätter and Heidelberger [11] first treated *cyclo*octatetraene with hydrogen bromide, and Reppe and his co-workers [1] identified the product as 1′-bromoethylbenzene. This rearrangement presumably involves addition of a proton to give the cation (XIV), followed by Wagner–Meerwein rearrangement to the cation (XV). Further rearrangement would give styrene which adds hydrogen bromide.

Cope, Nelson, and Smith [8] have repeated the work of Reppe and his co-workers [1] on the reactions of mercuric salts with *cyclo*octatetraene in various solvents and in two instances found erroneous identification of the products by the earlier workers. The product formed from the tetraene by mercuric acetate in acetic acid is the diacetate (XII; R = R′ = OAc), in methanol the product is *cyclo*hepta-2 : 4 : 6-trienealdehyde dimethyl acetal, and in water it is phenylacetaldehyde. These products are identical with those obtained in the solvolytic reactions of the dichloride. Although the nature of organic intermediates involved in reactions of mercuric complexes is not completely understood, it seems likely that very similar intermediates occur in the two sets of rearrangements.

## Experimental

*Oxidation of* 7 : 8-*Epoxy*cyclo*octa*-1 : 3 : 5-*triene.*—Potassium permanganate (1·5 g.) in N-sulphuric acid (68 ml.) was added quickly, with stirring, to a solution of the epoxide [1] (1·0 g.) in acetone (25 ml.) at 0°. The temperature rose to 30° and stirring was continued until the solution became clear. The mixture was then extracted several times with ether. These extracts contained an acid (40 mg.) and a neutral fraction (250 mg.), the latter consisting of some unchanged epoxide and an unidentified crystalline material. The aqueous residue was made alkaline with sodium hydroxide solution and extracted again with ether (4 × 150 ml.). These extracts were dried ($Na_2SO_4$) and evaporated. The residue of crude ditropyl ether was treated in dry ether with hydrogen bromide. The precipitated tropylium bromide was filtered off and dissolved in water (2 ml.), and a saturated aqueous picric acid solution added (5 ml.). Tropylium picrate was collected as yellow needles (170 mg., 7·2%), m. p. and mixed m. p. 98—99° (decomp.) after two crystallisations from water.

Similar experiments using hydrogen peroxide, lead tetra-acetate, or ceric ammonium nitrate gave mainly benzaldehyde and other unidentified products, but no tropylium salts.

*Rearrangement of* 2-(cyclo*Hepta*-2 : 4 : 6-*trienyl*)*propan*-2-*ol.*—Ethyl *cyclo*hepta-2 : 4 : 6-triene-carboxylate [5] (10·0 g.) in dry ether (20 ml.) was added at 5° with stirring to the Grignard reagent prepared from methyl iodide (20 g.) and magnesium (3·3 g.) in dry ether (200 ml.). The mixture

[11] Willstätter and Heidelberger, *Ber.*, 1913, **46**, 517.

XUM

was then refluxed with continuous stirring for 1 hr., cooled, and poured into ice-cold, saturated ammonium chloride solution. Washing the organic layer with water and evaporating it left a pale yellow oil which solidified. The *alcohol* crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 59—60° (7·8 g., 85%) (Found: C, 79·7; H, 8·4. $C_{10}H_{14}O$ requires C, 80·0; H, 9·3%), $\lambda_{max.}$ 256 mμ (log ε 3·51), $\lambda_{min.}$ 222 mμ (log ε 2·85).

The above alcohol (2·0 g.) was stirred vigorously for 10 min. with 10% hydrochloric acid (40 c.c.). Extraction with ether, followed by drying ($Na_2SO_4$) and fractionation, gave an almost quantitative yield of 2′-methylpropenylbenzene, b. p. 68·5—69°/0·6 mm., $n_D^{19}$ 1·5400 (Found: C, 90·7; H, 9·2. Calc. for $C_{10}H_{12}$: C, 90·9; H, 9·1%). The material rapidly decolorised bromine water and permanganate and showed the typical styrene ultraviolet absorption spectrum.

*Rearrangement of* cyclo*Hepta*-2 : 4 : 6-*trienyl Methyl Ketone.*—Anhydrous powdered cadmium chloride (10·3 g.) was added at 0° with stirring to methylmagnesium iodide (from 16·5 g. of methyl iodide and 2·75 g. of magnesium) in dry ether (250 ml.), and was followed by *cyclo*hepta-2 : 4 : 6-trienecarbonyl chloride [5] (9·2 g.) in ether (30 ml.). The mixture was stirred at room temperature for 1 hr., then excess of water was added. The ethereal solution was extracted with sodium carbonate solution and the organic layer fractionated. The *ketone* obtained (2·8 g., 30%) had b. p. 56—57°/0·6 mm., $n_D^{18}$ 1·5207 (Found: C, 80·4; H, 7·6. $C_9H_{10}O$ requires C, 80·6; H, 7·5%). Its *semicarbazone* formed plates (from alcohol–water), m. p. 175—176° (mixed m. p. with benzyl methyl ketone semicarbazone, 155—156°) (Found: C, 62·4; H, 6·9; N, 22·1. $C_{10}H_{13}ON_3$ requires C, 62·8; H, 6·8; N, 22·0%). The ketone readily decolorised bromine water and permanganate.

The ketone (0·2 g.) in 10% alcoholic hydrochloric acid (10 ml.) was warmed at 50° for a few minutes and 2 : 4-dinitrophenylhydrazine (0·3 g.) in the same solvent (10 ml.) was then added. Cooling and dilution afforded benzyl methyl ketone dinitrophenylhydrazone (0·35 g.), yellow needles (from ethyl acetate), m. p. and mixed m. p. 154—155°.

A similar rearrangement in acidic alcohol, followed by neutralisation, extraction with ether, and treatment of the extracted ketone in the usual way afforded benzyl methyl ketone semicarbazone as needles (from alcohol–water), m. p. and mixed m. p. 191—193°.

*Rearrangement of* cyclo*Hepta*-2 : 4 : 6-*trienealdehyde Dimethyl Acetal.*—The acetal was prepared from the dichloride (XII) and sodium methoxide and after several fractionations still contained a trace of chlorinated impurity.[1] The acetal (4·0 g.) was dissolved in absolute methyl alcohol (20 ml.), and three drops of concentrated sulphuric acid were added. The mixture was refluxed for 2 min., then cooled, made alkaline with sodium hydroxide solution, and extracted with ether. The crude product, after removal of the ether, was hydrogenated with palladised charcoal at atmospheric pressure in methanol (50 ml.) containing potassium hydroxide (0·5 g.) (absorption, 90 ml.). Filtration, removal of the solvent, and fractionation afforded phenylacetaldehyde dimethyl acetal, b. p. 52°/0·5 mm., $n_D^{20}$ 1·4930. The material showed an infrared spectrum identical with that of material prepared from phenylacetaldehyde and dimethyl sulphite.[12] If the hydrogenation step is omitted it is difficult to remove traces of chlorine-containing material from the product.

*Rearrangement of* 7 : 8-*Epoxy*cyclo*octa*-1 : 3 : 5-*triene.*—The epoxide (0·8 g.) was added in alcohol (10 ml.) to a solution at −5° of 2 : 4-dinitrophenylhydrazine (1·4 g.) in alcohol (85 ml.) containing 30% hydrochloric acid (7 ml.). The mixture was kept at −5° for 5 hr., then the red precipitate of *cyclo*hepta-2 : 4 : 6-trienealdehyde 2 : 4-dinitrophenylhydrazone was filtered off and washed successively with cold alcohol, water, aqueous sodium carbonate, and water. The crude product (dried *in vacuo* at room temperature) (1·32 g.), had m. p. 132—133° (decomp.). Four crystallisations from alcohol–benzene gave pure material as an orange-red powder, m. p. 136° (decomp.) alone or mixed with a specimen prepared by the method of Cope *et al.*[8] (Found: C, 55·8; H, 4·2; N, 18·6. Calc. for $C_{14}H_{12}O_4N_4$: C, 56·0; H, 4·0; N, 18·7%), $\lambda_{max.}$ 260, 273, and 356 mμ (log ε 3·96, 4·11, 4·35 in chloroform).

A similar experiment at 70° for 15 min. gave mainly phenylacetaldehyde 2 : 4-dinitrophenylhydrazone.

*Methanolysis of the Dichloride of* cyclo*Octatetraene.*—Reaction of the dichloride with methanol was conducted as described by Reppe *et al.*[1] The final product was carefully fractionated and found to be principally one compound. The middle fraction had $n_D^{20}$ 1·4931, the infrared spectrum of phenylacetaldehyde dimethyl acetal, and b. p. 49·5°/0·4 mm. (Found: C, 72·0; H, 8·5; OMe, 36·9. Calc. for $C_{10}H_{14}O_2$: C, 72·3; H, 8·4; OMe, 37·3%).

[12] Voss, *Annalen*, 1931, **485**, 283.

*Phenylacetaldehyde Dimethyl Acetal from β-Methoxystyrene.*—β-Methoxystyrene was prepared from phenylacetylene and potassium methoxide as described by von Auwers,[13] but the yield was increased by continuous stirring. A solution of β-methoxystyrene (6·0 g.) in absolute methyl alcohol (60 ml.) containing 100% sulphuric acid (0·5 c.c.) was refluxed for 3 min. After cooling, the mixture was made alkaline. Extraction with ether and working up in the usual way gave phenylacetaldehyde dimethyl acetal (4·0 g.; $n_D^{20}$ 1·4931). The middle fraction had an infrared spectrum identical with that of authentic material.

*Phenylglycol Dimethyl Ether.*—Phenylglycol (prepared from styrene dibromide [14]) was methylated in good yield with methyl sulphate as described for glucose.[15] The product had b. p. 55°/0·5 mm., $n_D^{20}$ 1·4948 (Found: C, 72·4; H, 8·6; OMe, 35·8. Calc. for $C_{10}H_{14}O_2$: C, 72·3; H, 8·4; OMe, 37·3%). The material has a very similar odour to that of phenylacetaldehyde dimethyl acetal but does not give phenylacetaldehyde dinitrophenylhydrazone after hydrolysis with warm alcoholic acids. More vigorous hydrolysis of the dimethyl ether is reported to yield phenylacetaldehyde.

We are grateful to the University of London for an I.C.I. Research Fellowship (to R. P.) and for a D.S.I.R. maintenance grant (to C. R. G.). We thank Professor M. J. S. Dewar for reading the manuscript and Messrs. May and Baker Ltd. for a gift of *cyclo*octatetraene.

QUEEN MARY COLLEGE, (UNIVERSITY OF LONDON),
MILE END ROAD, LONDON, E.1.
[Present address (R. P.): UNIVERSITY OF TEXAS, AUSTIN 12, TEXAS, U.S.A.]

[*Received, August 8th*, 1957.]

[13] von Auwers, *Ber.*, 1911, **44**, 3519.
[14] Evans and Morgan, *J. Amer. Chem. Soc.*, 1913, **35**, 54.
[15] West and Holden, *Org. Synth.*, Coll. Vol. III, 1955, p. 800.

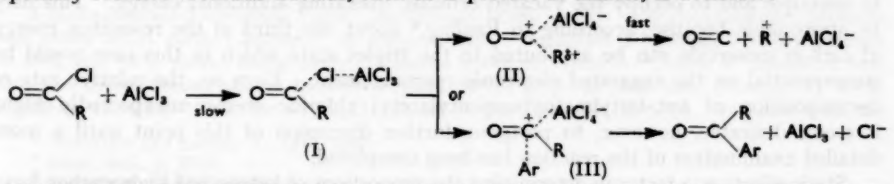
---

## 113. *The Reaction between Aromatic Compounds and Derivatives of Tertiary Acids. Part X.* Elimination of Carbon Monoxide from Some Highly Alkylated Acetyl Chlorides.*

By MICHAEL E. GRUNDY, WEI-HWA HSÜ, and EUGENE ROTHSTEIN.

The replacement of methyl by ethyl in pivaloyl chloride increases the rate of the aluminium-catalysed elimination of carbon monoxide three- to four-fold for each replacement. *tert.*-Butylmethyl*neo*pentylacetyl chloride reacts over 300 times as fast as pivaloyl chloride. This increase is probably associated with the inductive effect of alkyl. It is possible that steric effects are largely responsible for the relative amounts of ketone and hydrocarbon which are formed when anisole is the solvent. In general, the kinetics of the above reactions closely resemble those of pivaloyl chloride.

INVESTIGATION of the kinetics of the catalysed elimination of carbon monoxide from derivatives of tertiary acids has hitherto been concerned with those of pivalic acid.[1-3] The rate-determining step is the production of a dipolar ion between the catalyst and the acid derivative followed, in the normal case, by the fast elimination of carbon monoxide or alternatively, by the formation of a ketone, the latter reaction occurring only when a specially reactive aromatic nucleus, such as is present in anisole, is available:




* Part IX, *J.*, 1956, 4561.

[1] Rothstein and Saville, *J.*, 1949, 1954.
[2] Grundy, Hsü, and Rothstein, *J.*, 1956, 4558.
[3] *Idem*, *J.*, 1956, 4561.

The initial reaction requires separation of halogen (it is not suggested that the chlorocarbonyl group separates as such) and it is evident that electron-releasing groups should accelerate it irrespective of the relative stabilities of entities (II) and (III). Hyperconjugation with an α-alkyl group cannot affect the formation of the complex (I) but might lower the energy of (II) compared with (III), *i.e.*, increase the proportion of carbon monoxide relative to ketone: $O{=}\overset{\curvearrowleft}{C}{-}CR_2{-}\overset{\curvearrowleft}{CH_2}{-}H$ but this would not be observable kinetically because it is not for this reaction the rate-determining stage. H. C. Brown and his collaborators [4] believe that first-order solvolysis of highly branched alkyl halides results from the tendency of the strained tetrahedral carbon atom to assume the less strained form of a planar carbonium ion. Such steric effects though they may influence ketone formation, cannot operate on the halogen atom in acid chlorides and consequently it appears reasonable to infer that the principal factor in the detachment of halogen from the chlorocarbonyl group must be inductive.

The change in reaction rate when a methyl group in pivalic acid is replaced by ethyl and by other groups has been studied. The reaction constant is increased 3—4-fold for each such replacement and over 300-fold when two methyl groups are substituted by *tert.*-butyl and by *neo*pentyl groups, respectively. These relative rates are set out in Table 1, but owing to the widely differing reaction rates for differing alkylation, it has been necessary to measure them at two concentrations. The third column combines the results of the first two, an arithmetical average being taken for the figure for diethylmethyl- relative to ethyldimethyl-acetyl chlorides.

TABLE 1. *Relative reaction rates for the decomposition of alkylated acetyl chlorides,* RR′R″COCl, *in benzene* (Pe = *neo*pentyl).

| | | | $AlCl_3$ (mole/l.) | | |
|---|---|---|---|---|---|
| R | R′ | R″ | 0·05 | 0·025 | Rel. rates |
| Me | Me | Me | 0·265 | — | 1 |
| Et | Me | Me | 1 | 1 | 3·8 |
| Et | Et | Me | 4·74 | 5·42 | 19·3 |
| Et | Et | Et | — | 19·28 | 73·3 |
| Bu | Pe | Me * | — | 84·78 | 322 |

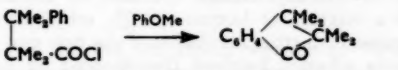
* Unpublished work with W. Bleazard. Details of experiments with this acid chloride will be given in a separate communication.

Comparison of these results with those obtained [5] by the solvolysis of tertiary alkyl halides at 25° ($CMe_3Cl$, 1; $CEtMe_2Cl$, 1·63; $CEtMeCl$, 2·53; $CEt_3Cl$, 3·0; $CMe_2PeCl$, 20) suggests that electron accession to carbonyl carbon not only promotes the separation of chlorine directly, but also decreases the mesomerism inherent in the chlorocarbonyl group, $\overset{\curvearrowright}{Cl}{-}CR{=}\overset{\curvearrowright}{O} \longleftrightarrow \overset{\curvearrowleft}{Cl}{=}CR{-}\overset{\curvearrowleft}{O}$. Consequently chlorine is less tightly attached to carbon and the unshared *p* electrons are more strongly directed for bond formation with the catalyst. Moreover as the chlorine electrons leave vacant the *p* orbitals on carbon, those of the σ-carbon–carbon bond by which carbonyl is attached to the remainder of the molecule tend to uncouple and to occupy the vacated orbitals, liberating additional energy. This may be appreciable because, according to Pauling,[6] about one third of the resonance energy of carbon monoxide can be attributed to the triplet state which in this case would be consequential on the suggested electronic rearrangement. Even so, the relative rate of decomposition of *tert.*-butylmethyl*neo*pentylacetyl chloride seems unexpectedly high; it seems desirable, however, to postpone further discussion of this point until a more detailed examination of the reaction has been completed.

Steric effects as a factor in determining the proportions of ketone and hydrocarbon have

[4] See for instance, Brown and Moritani, *J. Amer. Chem. Soc.*, 1955, **77**, 3623.
[5] Hughes, Ingold, and Shiner, *J.*, 1953, 3827.
[6] Pauling, "The Nature of the Chemical Bond," Cornell University Press, 2nd Edn., 1945, p. 135.

already been mentioned. The ease of cyclisation of tertiary phenylpropionyl and phenylbutyryl halides was taken by Rothstein and Saville [7] as an indication that proximity of the reacting groups was especially important in this respect. They also noted [8] that tetramethylsuccinic anhydride yields exclusively the ketone (IV) with anisole but on the other hand one of us observed that in this solvent ααββ-tetramethyl-β-phenylpropionyl chloride affords only the cyclic ketone (V): [9]




In neither case is any carbon monoxide eliminated and it is probable that if cyclisation were inhibited by the insertion of a *p*-nitro-group (as with *p*-nitrophenylpivaloyl chloride [7]) the open-chain *p*-methoxyphenyl 2 : 2 : 3 : 3-tetramethyl-3-phenylpropyl ketone would result. Alkylated phenyl groups are less nucleophilic than *p*-methoxyphenyl and therefore in these cases anisole is sterically prevented from closely approaching the chlorocarbonyl group. Alkylation in the β-position is important in this connection because 64% of open-chain ketone is formed from αα-dimethyl-β-phenylpropionyl chloride.[9]

The relevance of the foregoing to the present work is that it has now been found that triethylacetyl chloride and anisole afford a small proportion of triethyl-*p*-methoxyphenylmethane in addition to the main product of triethylmethyl *p*-methoxyphenyl ketone whilst *tert.*-butylmethyl*neo*pentylacetyl chloride and anisole yield only the hydrocarbon. It is not yet known whether rearrangement occurs with the latter: it does not appear to do so with the triethyl derivative. Non-production of ketone in the above experiment has made it possible to ascertain whether the use of anisole as a solvent influences the rate of elimination of carbon monoxide. The implicit assumption made in Part IX that solvent effects were not responsible for the diminution of this rate with increasing concentrations of anisole has been confirmed accordingly by carrying out the reaction between *tert.*-butylmethyl*neo*pentylacetyl chloride (0·025 mole/l.), and aluminium chloride (0·0125 mole/l.) in pure benzene, in a solution of anisole in benzene (0·025 mole/l.) and in pure anisole. The rate-constants were 0·0584, 0·0556, and 0·0587 min.$^{-1}$, respectively.

Only the estimations of carbon monoxide were used for the calculation of the rate-constants in Table 1. The titration method (Part VIII [2]) was unreliable for these rapid reactions, but was of service in indicating that the connection between rate-constant and concentrations of reactants was analogous to that already found for pivaloyl chloride. This is discussed in the kinetic section.

## Experimental

*Preparation of Materials.*—*αα-Dimethylbutyric acid* (*ethyldimethylacetic acid*). This was obtained in 40% yield, b. p. 92·5°/20 mm., by passing carbon dioxide into ethereal 1 : 1-dimethylpropylmagnesium chloride.[10] The acid chloride (yield 90%; b. p. 132°) was prepared from the acid and 50% excess of thionyl chloride at room temperature.

*3-Methylpentane-3-carboxylic acid* (*diethylmethylacetic acid*). Ethylmagnesium bromide and either ethyl methyl ketone [11] or ethyl acetate [12] furnished 3-hydroxy-3-methylpentane in 80% and 65% yields, respectively. Gaseous hydrogen chloride [13] below 0° converted this into the corresponding chloro-derivative (yield 83%), b. p. 37°/140 mm. (Found: C, 60·3; H, 10·5; Cl, 29·0. Calc. for $C_6H_{13}Cl$: C, 59·8; H, 10·8; Cl, 29·5%). Saturation of the

[7] Rothstein and Saville, *J.*, 1949, 1946.
[8] *Idem, ibid.*, p. 1950.
[9] Rothstein, *J.*, 1951, 1459.
[10] Gilman and Zoellner, *Rec. Trav. chim.*, 1928, **47**, 1058.
[11] Whitmore and Lewis, *J. Amer. Chem. Soc.*, 1942, **64**, 2964
[12] Wilcox and Brunel, *ibid.*, 1916, **38**, 1838.
[13] Schreiners, *J. prakt. Chem.*, 1910, **82**, 295.

XUM

corresponding Grignard reagent with carbon dioxide afforded 3-methylpentane-3-carboxylic acid (yield, 40%), b. p. 108°/13 mm. The acid chloride (b. p. 54°/19 mm.) was prepared by using thionyl chloride (90% yield).

*3-Ethylpentane-3-carboxylic acid* (*triethylacetic acid*). Several methods for the synthesis of this acid were attempted. That from tetraethylethylene glycol [14] was unsatisfactory because of the poor yield (25%) of starting material obtained by the reduction of diethyl ketone. Isomerisation of the glycol to 4 : 4-diethylhexan-3-one (yield, 45%) was carried out with ice-cold concentrated sulphuric acid, and the ketone was oxidised by boiling nitric acid to triethylacetic acid (yield, 60%).

The hydrolysis of diethylbutyronitrile, obtained by the alkylation of acetonitrile,[15] was inconvenient because a mixture of butyro- (29%), ethylbutyro- (21%), and diethylbutyronitriles (11%) was obtained; further alkylation of the first two nitriles was extremely difficult.

The synthesis finally adopted followed that devised by Doering and Wilberg [16] for the preparation of other tertiary acids from alkylated acetoacetic esters.

A solution of ethyl diethylacetoacetate (60 g.) in alcohol (50 c.c.) was mixed with Raney nickel (3 g.) and reduced at 110° for 10 hr. under 60—90 atm. pressure. Fractionation from unchanged ester (20 g.) afforded *ethyl αα-diethyl-β-hydroxybutyrate* (40 g.; 66%), b. p. 97°/9 mm. (Found: C, 63·7; H, 10·6. $C_{10}H_{20}O_3$ requires C, 63·9; H, 10·6%), $d_4^{18\cdot4}$ 0·9731, $n_4^{17\cdot4}$ 1·4425.

The above hydroxy-ester (32 g.) was gradually added to a stirred suspension of phosphorus pentoxide (37 g.) in dry benzene (30 c.c.). The solvent was distilled off and the residue extracted first with benzene and then with alcohol. The combined extracts and distillate yielded *ethyl diethylvinylacetate* (20 g.; 71%), b. p. 76°/16 mm. (Found: C, 70·5; H, 10·4. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6%), $d_4^{17\cdot2}$ 0·8900, $n_D^{17\cdot3}$ 1·4332. Hydrogenation of this ester (13·4 g.) in alcohol (40 c.c.) with Raney nickel (1·2 g.) for 3 hr. at 2—3 atm. yielded ethyl triethylacetate (12 g.; 89%), b. p. 63°/18 mm. (Found: C, 70·0; H, 11·6. Calc. for $C_{10}H_{20}O_2$: C, 69·8; H, 11·6%), $d_4^{16}$ 0·8837, $n_D^{17\cdot2}$ 1·4200. Hydrolysis with methanolic potassium hydroxide afforded the acid (93%), b. p. 119°/14 mm. (Found: C, 66·8; H, 10·9. Calc. for $C_8H_{16}O_2$: C, 66·6; H, 11·2%). Excess (50%) of thionyl chloride at room temperature furnished the acid chloride (87%), b. p. 62°/12 mm. (Found: C, 59·5; H, 9·2; Cl, 21·9. Calc. for $C_8H_{15}OCl$: C, 59·5; H, 9·5; Cl, 21·1%).

*Friedel–Crafts Condensations with 3-Ethylpentane-3-carbonyl Chloride.*—(1) *In benzene at* 0°. The product obtained by stirring the acid chloride (10 g.), aluminium chloride (10 g.), and benzene (60 c.c.) at 0° consisted mainly of 3-ethyl-3-phenylpentane (2·86 g.), two unidentified unsaturated hydrocarbons (1·1 g. in all), b. p. 142—148°/2 mm. and b. p. 150—170°/2 mm., severally, and much non-volatile tar.

(2) *In benzene at* 20—22°. A solution of aluminium chloride (16·75 g., 0·125 mole) in nitrobenzene (100 c.c.) was added to a stirred solution of the acid chloride (20·1 g., 0·125 mole) in benzene (800 c.c.). The liquid was left overnight at room temp. and then decomposed by ice and dilute acid. The product (26·8 g.), b. p. 90—92°/9 mm., was heated on a steam-bath and stirred with equal volumes (1550 c.c.) of 15% titanous chloride and concentrated hydrochloric acid. The yield of nitrobenzene-free 3-ethyl-3-phenylpentane, b. p. 97°/9 mm., was 12 g. (54·5%). The previously recorded [17] b. p. was 107·5°/20 mm. (Found: C, 88·2; H, 11·5. Calc. for $C_{13}H_{20}$: C, 88·6; H, 11·4%). The infrared absorption curve showed the absence of a carbonyl group and had a number of low-intensity bands between 2000 and 1660 cm.$^{-1}$, the most prominent being at 1961, 1876, 1805, 1754, and 1704 cm.$^{-1}$. The absence of high-intensity peaks in the 1250—1200 cm.$^{-1}$ region characteristic of quaternary carbon appears to be typical of highly alkylated benzenes. Frequencies and approximate extinction coefficients measured in 0·05 molar solutions in carbon tetrachloride, a 0·8 mm. cell being used with quartz windows for the 3000 cm.$^{-1}$ region, are given in Table 2 and are compared with those of *n*-butylbenzene. The latter (one methyl group) shows the expected differences from ethylphenylpentane (three methyl groups) and also from 3-ethyl-3-*p*-methoxybenzoylpentane (see below).

(3) *In anisole.* The reaction was carried out as with benzene but nitrobenzene was not used. A small quantity of *3-ethyl*-3-p-*methoxyphenylpentane*, b. p. 142—143°/15 mm., 88—92°/0·30 mm., was isolated (Found: C, 81·6; H, 10·7%; *M*, 204. $C_{14}H_{22}O$ requires C, 81·6; H, 10·7%; *M*, 206). The main product (90% yield) was *3-ethyl*-3-p-*methoxybenzoylpentane*, b. p.

[14] Meerwein, *Annalen*, 1919, **419**, 153.
[15] Ziegler and Ohlinger, *ibid.*, 1932, **495**, 84; Schuerch and Huntress, *J. Amer. Chem. Soc.*, 1948, **70**, 2824.
[16] Doering and Wiberg, *ibid.*, 1950, **72**, 2608.
[17] Huston, Fox, and Binder, *J. Org. Chem.*, 1938, **3**, 251.

TABLE 2. C–H *Stretching frequencies for* 1-*phenylbutane*, 3-*ethyl*-3-*phenylpentane*, *and* 3-*ethyl*-3-p-*methoxybenzoylpentane.*

| | *n*-BuPh | | $CEt_3Ph$ | | $CEt_3{\cdot}CO{\cdot}C_6H_4{\cdot}OMe$ | |
|---|---|---|---|---|---|---|
| Assignment [18] | cm.$^{-1}$ | ε | cm.$^{-1}$ | ε | cm.$^{-1}$ | ε |
| Ph | 3086 | 29 | 3088 | 29 | 3081 | 20 |
| Ph | 3063 | 35 | 3062 | 36 | 3070 | 20 |
| Ph | 3027 | 53 | 3028 | 36 | 3042 | 22 |
| Me | 2956 | 104 | 2964 | 127 | 2972 | 199 |
| Me (?) | — | — | — | — | 2944 | 157 |
| $CH_2$ | 2928 | 123 | 2933 | 102 | 2882 | 99 |
| Me | 2871 | 53 | 2874 | 69 | 2868 | 58 |
| $CH_2$ | 2858 | 61 | — | — | 2841 | 54 |

129°/0·13 mm. (Found: C, 77·0; H, 9·4. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·4%). Strong infrared carbonyl absorption was shown at 1672 cm.$^{-1}$ and intense peaks at 1258 and 1238 cm.$^{-1}$ due to quaternary C–C skeletal vibrations also appeared in the infrared spectrum.

*Kinetic Measurements* (cf. Part VIII).—(1) *Carbon monoxide method.* The increase in reaction rate in passing from one homologue to the next was about four-fold so that although the variation of the individual " runs " was of the order of 10%, the overall aspects of the results are quite clear. Some individual measurements are given in Table 3 together with the derived first-order constants. The values in parentheses indicate the percentage of the reaction used for the calculation. Table 4 gives the complete results, the constants being the mean of 3 or 4 determinations. In all cases, equal concentrations of acid chloride and catalyst were employed.

TABLE 3. *Carbon monoxide (mole/l.) evolved from acid chlorides* RR'R"C·COCl.

| [$AlCl_3$] (mole/l.): | 0·050 | | 0·025 | | | |
|---|---|---|---|---|---|---|
| R, R', R": | EtMeMe | EtEtMe | EtEtMe | EtEtEt | | Bu$^t$MePe |
| *t* (min.) | | | | | *t* (min.) | |
| 6 | 0·0030 | 0·0101 | 0·0022 | 0·0044 | 2 | 0·0019 |
| 12 | 0·0061 | 0·0210 | 0·0040 | 0·0115 | 4 | 0·0102 |
| 18 | 0·0087 | 0·0278 | 0·0057 | 0·0149 | 6 | 0·0169 |
| 24 | 0·0111 | 0·0326 | 0·0070 | 0·0171 | 8 | 0·0196 |
| 30 | 0·0134 | 0·0359 | 0·0090 | 0·0185 | 10 | 0·0210 |
| 36 | 0·0152 | 0·0383 | 0·0102 | 0·0195 | 12 | 0·0215 |
| 42 | 0·0169 | 0·0400 | 0·0113 | 0·0202 | — | — |
| 48 | 0·0184 | 0·0413 | 0·0121 | 0·0206 | — | — |
| 54 | 0·0197 | 0·0421 | 0·0128 | — | — | — |
| 60 | 0·0210 | 0·0426 | 0·0135 | — | — | — |
| 66 | 0·0220 | 0·0430 | 0·0141 | — | — | — |
| $10^2k_1$ (min.$^{-1}$) | 0·82(42) | 4·49(65) | 1·32(46) | 5·44(59) | — | 25·45(78) |

TABLE 4. *First-order constants for acid chlorides* RR'R"C·COCl.

| R, R', R": | MeMeMe * | EtMeMe | | EtEtMe | | EtEtEt | | Bu$^t$MePe |
|---|---|---|---|---|---|---|---|---|
| [$AlCl_3$], mole/l. | 0·05 | 0·05 | 0·025 | 0·05 | 0·025 | 0·025 | 0·0167 | 0·025 |
| $10^2k_1$ (mean), min.$^{-1}$ | 0·223 | 0·840 | 0·272 | 3·98 | 1·475 | 5·231 | 3·55 | 23·060 |

* Part IX.

(2) *Acid titration method.* These measurements with large excesses of acid chloride were not very accurate because of the large volumes of carbon monoxide evolved in the initial stages of the reaction, and since repetition of individual " runs " was impracticable, the values of the reaction constants were only approximate. Nevertheless the following conclusions could be made: (*a*) aluminium chloride is unaltered by the main reaction and can catalyse the decomposition of more than ten times its molecular proportion of acid chloride. (*b*) Side-reactions (*e.g.*, the formation of the ketone, $CR_2{=}CH{\cdot}CO{\cdot}CR_2Me$) deactivate the catalyst as the reaction progresses [19] and this deactivation decreases as the molecular proportion of the acid halide decreases; when this proportion is small [*e.g.*, the reaction between triethylacetyl chloride (0·08 mole/l.) and aluminium chloride (0·025 mole/l.)] there is no deactivation. (*c*) Although in most cases it was not possible to measure the initial rates of the reactions, comparison with the corresponding carbon monoxide determinations at equivalent points of the reactions showed

[18] Fox and Martin, *Proc. Roy. Soc.*, 1938, *A*, **167**, 257; 1940, *A*, **175**, 208.
[19] Grundy, Hsü, and Rob[illegible], *J.*, 1952, 4136.

TABLE 5. *Progress of reaction for (A) ethyldimethyl- and (B) diethylmethyl-acetyl chlorides.* $[AlCl_3] = 0{\cdot}05$ *mole/l.*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *A*, Time (min.) ..... | 0 | 3·2 | 10·6 | 24·5 | 61·4 | 115 | 181 | 301 |
| Reaction (%) ..... | 17·5 | 25·4 | 28·9 | 34·6 | 48·6 | 62·9 | 72·4 | 79·7 |
| *B*, Time (min.) ..... | 0 | 2·5 | 6·4 | 12·0 | 21·6 | 37·6 | 73·6 | 180·5 |
| Reaction (%) ..... | 43·8 | 45·7 | 47·6 | 61·6 | 75·5 | 80·6 | 91·1 | 94·0 |

TABLE 6. *Initial and total reactions, and some first-order constants for ethyldimethyl-, diethylmethyl-, and (C) triethylacetyl-chlorides.*

| $[AlCl_3]$, mole/l. | Reaction before 1st titration (%) | | | Total reaction (%) | | | $10^2k_1$ (min.$^{-1}$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *A* | *B* | *C* | *A* | *B* | *C* | *A* | *B* | *C* | $n_A$ ‡ |
| 0·0315 | 4 | 23 | — | 60 | 96 | — | 0·375 | 2·2 | — | — |
| 0·05 | 17 | 44 | — | 80 | 94 | — | 0·680 | — | — | 1·28 |
| 0·05 * | 13 | 34 | — | 63 | 81 | — | 0·442 | — | — | — |
| 0·063 | 13 | 45 | 81·5 | 94 | 97 | 100 | 1·34 | — | — | 1·84 |
| 0·126 | 37 | 85 | — | 97 | 98 | — | 4·24 | — | — | 1·75 |
| 0·025 † | — | — | 9 | — | — | 94 | — | — | 5·44 | — |

* [Acid chloride] = 0·630 mole/l. † $[CEt_3{\cdot}COCl] = 0{\cdot}08$ mole/l.
‡ Order (for *A*) with respect to catalyst.

that the time–concentration curves were nearly identical in slope. (*d*) For ethyldimethylacetyl chloride the order with respect to catalyst approaches 2 (as for pivaloyl chloride) and it is probable that this is also true for the other acid halides. The reaction rates are comparable for constant concentrations of the catalyst only; consequently the exact dependence of rate on the latter cannot be accurately derived from the available data and therefore no attempt has been made to obtain the third-order constants, involving both the catalyst and the acid chloride. The next two tables give some of the details obtained by the titration method. Initial concentrations were $[CEtMe_2{\cdot}COCl] = [CEt_2Me{\cdot}COCl] = [CEt_3{\cdot}COCl] = 0{\cdot}315$ mole/l., unless otherwise indicated. These halides are labelled *A*, *B*, and *C*, respectively.

THE UNIVERSITY, LEEDS.

[*Received, August 28th,* 1957.]

## 114. *Quantitative Aspects of the Acid Reversion of Glucose.*

By STANLEY PEAT, W. J. WHELAN, T. E. EDWARDS, and (MRS.) O. OWEN.

The products formed when glucose is heated in aqueous sulphuric acid, with or without pretreatment with formic acid, have been separated and estimated. The major products are 1 : 6-anhydro-β-D-gluco-pyranose and -furanose, while the remainder consists of the group of glucose disaccharides, in which isomaltose and gentiobiose predominate. The amounts of sugars so formed provide a guide to the quantities of reversion products likely to be encountered as artefacts in the examination of the structures of polyglucoses by the method of partial acidic hydrolysis.

WHEN exposed to acid sugars undergo inter- and intra-molecular elimination of water, between the hemiacetal and (mainly) the primary hydroxyl group. This acid-catalysed reversion of sugars, and of glucose in particular, has recently been studied, first with respect to the synthesis of large polymers with dextran-like properties,[1–3] and secondly as a factor in the linkage analysis [4] of polysaccharides by partial acidic hydrolysis. The present work is concerned with the second aspect.

Thompson, Wolfrom, and Quinn [5] found that when glucose was heated in 0·082N-hydrochloric acid at 97° for 10 hr. isomaltose and gentiobiose were formed in amounts which were approximately equal and in linear relation to the concentration of glucose over

[1] Pacsu and Mora, *J. Amer. Chem. Soc.*, 1950, **72**, 1045.
[2] Ricketts, *J.*, 1954, 4031.
[3] Kent, *Biochem. J.*, 1953, **55**, 361.
[4] Peat, Whelan, and Edwards, *J.*, 1955, 355.
[5] Thompson, Wolfrom, and Quinn, *J. Amer. Chem. Soc.*, 1953, **75**, 3003.

the range 0·4—10%. Previously, Wolfrom and his collaborators [6] had isolated isomaltose from an acid hydrolysate of waxy-maize starch and Thompson *et al.*[5] concluded that the isomaltose found in the polysaccharide hydrolysates could not be a reversion artefact since the yield was 200 times that obtained from the reversion of glucose under comparable conditions. Results reported by Bacon and Bacon [7] in respect of isomaltose formed from glucose and from glycogen under the same acidic conditions were similar except that the yield of isomaltose from glycogen was only about eight times that formed from glucose.

While isomaltose and gentiobiose are the major disaccharide products of reversion it is known that hydroxyl groups other than primary can condense with the reducing group. There are, in all, eleven disaccharides which could be formed from two glucopyranose units and Thompson, Anno, Wolfrom, and Inatome [8] isolated seven of these (as the crystalline octa-acetates) from a glucose–acid reaction mixture. These were isomaltose, gentiobiose, maltose, cellobiose, nigerose, sophorose, and ββ-trehalose. In addition, the product of an intramolecular elimination of water, namely, 1 : 6-anhydro-β-D-glucopyranose (lævoglucosan), was obtained.

Our interest in this problem arises from structural studies on glucans (cf. ref. 4) in which sulphuric acid or formic acid–sulphuric acid has been used to hydrolyse the polysaccharides. Accordingly, we have examined the formation of reversion products from glucose under conditions identical with those used to hydrolyse the polysaccharides. A scheme of fractionation, based on charcoal and paper chromatography and paper electrophoresis, has made possible the separation and estimation of the products, and has provided further information on the products of intramolecular elimination of water.

*Conditions of Acid Reversion.*—Two sets of conditions were chosen. The reaction studied in greater detail was the reversion occurring in 0·33N-aqueous sulphuric acid at 100°. These conditions have been used by us for the hydrolysis of amylose,[9] laminarin,[10] lichenin,[11] isolichenin,[12] dextran,[13] and yeast glycogen.[4] These polysaccharides are soluble in aqueous acid. Yeast glucan, however, is insoluble in this medium but can be dissolved and degraded in hot formic acid to water-soluble fragments, and the hydrolysis can then be continued in 0·33N-sulphuric acid.[14]

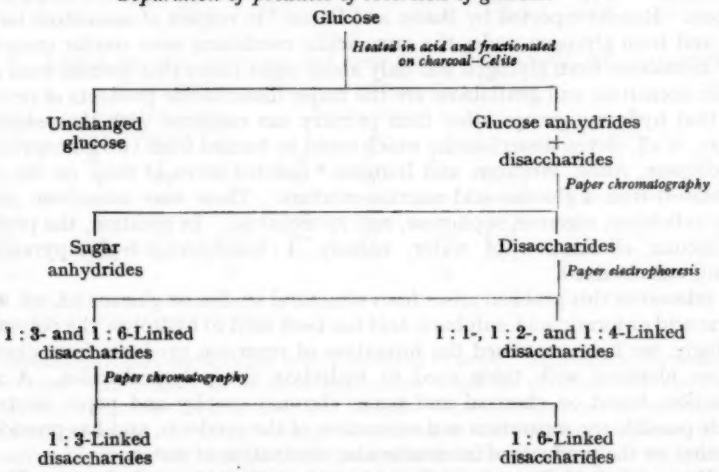
The fractionation scheme, which is summarised below, involved the following steps: (1) The neutralised solution of acid-treated glucose was passed through charcoal–Celite; irrigation with water then removed salts and unchanged glucose; thereafter the reversion products were displaced from the column with 25% aqueous ethanol. [In some experiments the column was eluted first with 7·5% ethanol, to displace glucose anhydrides and disaccharides and then with 15% ethanol to displace trisaccharides. The amounts of the latter formed under these conditions were, however, negligible.] (2) The reversion products were separated by thick-paper chromatography into sugar anhydrides and disaccharides. (3) The disaccharide mixture was separated into two fractions by electrophoresis on thick paper in borate buffer. It was known from earlier studies [15] that the fraction of lower $M_G$ value would contain 1 : 1-, 1 : 2-, and 1 : 4-linked diglucoses, if these had been formed, whereas the faster-moving fraction would contain the 1 : 3- and 1 : 6-linked sugars. (4) The fraction of higher $M_G$ value was further resolved by paper chromatography into two sub-fractions, the first of which would contain the 1 : 6-linked anomers, isomaltose and gentiobiose, and the second, the 1 : 3-linked, nigerose and laminaribiose. These anomers were not separated in the case of the sulphuric acid reversion but with the

[6] Wolfrom, Tyree, Galkowski, and O'Neill, *J. Amer. Chem. Soc.*, 1951, **73**, 4927.
[7] Bacon and Bacon, *Biochem. J.*, 1954, **58**, 396.
[8] Thompson, Anno, Wolfrom, and Inatome, *J. Amer. Chem. Soc.*, 1954, **76**, 1309.
[9] Whelan, Bailey, and Roberts, *J.*, 1953, 1293.
[10] Peat, Whelan, and Lawley, *J.*, 1958, in the press.
[11] Peat, Whelan, and Roberts, *J.*, 1957, 3916.
[12] Peat, Whelan, and Morgan, to be published.
[13] Turvey and Whelan, *Biochem. J.*, 1957, **67**, 49.
[14] Peat, Whelan, and Edwards, to be published.
[15] Peat, Whelan, and Hinson, *Nature*, 1952, **170**, 1056; *Chem. and Ind.*, 1955, 385.

XUM

products formed by the combined action of formic acid and sulphuric acid the sub-fractionation on paper was carried further in that isomaltose was separated from gentiobiose on charcoal.

*Separation of products of reversion of glucose.*




*Quantitative Estimation of the Products of Reversion.*—(a) *Glucose anhydrides.* This product was first encountered, during trial experiments with formic acid–sulphuric acid, in the fraction (of negative optical rotation) eluted from the charcoal immediately before the disaccharide fraction. The material had an $R_F$ value almost twice that of glucose and could not be located on paper by reducing-sugar sprays but was by silver nitrate–sodium hydroxide,[17] with which it reacted slowly. This is characteristic of a non-reducing sugar. The non-reducing character was confirmed by quantitative measurement with an alkaline copper reagent. The suggestion that this substance might be lævoglucosan was made by Professor E. J. Bourne. The specific optical rotation (−41·4°) was, however, appreciably less negative than that of 1 : 6-anhydro-β-D-glucopyranose (−66·3°) [18] and it seemed possible that some of the furanose form [19] (+42·5°) might be present. A ratio of pyranose : furanose of 77 : 23 would accommodate the observed $[\alpha]_D$ values. This surmise was confirmed when the substance was oxidised with periodate. (The pyranose form consumes 2 moles of periodate and releases 1 mole of formic acid; the furanose form is not oxidised.[19]) On the assumption that only lævogluco-pyranosan and -furanosan were present in this fraction the periodate consumption and formic acid liberation corresponded to pyranose : furanose ratios of 78 : 22 and 80 : 20, respectively, in good agreement with the calculation based on optical rotation. Accordingly, in the later quantitative studies of acid reversion, the weight yield of the anhydride fraction was estimated by acidic hydrolysis to glucose (measured by copper-reducing power) and its composition by measurement of $[\alpha]_D$ value. The results are shown in the Table.

(b) *Disaccharides.* The weights of sugars present in all fractions were estimated by acidic hydrolysis to glucose. In four cases it was possible to calculate the weights of individual sugars. As has been indicated, the 1 : 6- and 1 : 3-linked disaccharides were obtained in anomeric pairs, *viz.*, isomaltose + gentiobiose and nigerose + laminaribiose. The members of each pair have widely different $[\alpha]_D$ values and therefore the amounts of the individual sugars could be accurately assessed by comparing the $[\alpha]_D$ value of the mixture with those of the anomers. Incidentally, for preparative purposes, the disaccharide anomers are easily separable by charcoal–Celite fractionation; the α-linked form is eluted first.

The fraction containing the 1 : 1-, 1 : 2-, and 1 : 4-linked sugars was not analysed for

*Products of reversion of glucose by acid (% basis).*

| | Glucose (1·0%) heated in 0·33N-sulphuric acid | | | Glucose heated in (i) formic acid and (ii) aqueous sulphuric acid |
|---|---|---|---|---|
| | 2 hr. | 5 hr. | 10 hr. | |
| Glucose anhydrides * ..... | 0·375 (53 : 47) | 0·430 (69 : 31) | 0·510 (66 : 34) | 1·35 (82 : 18) |
| Disaccharides: | 0·164 | 0·234 | 0·307 | 1·37 |
| Isomaltose ..... | 0·052 | 0·074 | 0·105 | 0·249 † |
| Gentiobiose ..... | 0·032 | 0·053 | 0·071 | 0·246 ‡ |
| Nigerose ..... | 0·014 | 0·015 | 0·025 | 0·119 |
| Laminaribiose ..... | 0·011 | 0·013 | 0·008 | 0·087 |
| Maltose + cellobiose ..... | 0·021 | 0·040 | 0·054 | 0·185 |
| Kojibiose + sophorose + trehaloses ..... | 0·034 | 0·039 | 0·044 | 0·487 |
| Total ..... | 0·539 | 0·664 | 0·817 | 2·72 |

* Figures in parentheses are the ratios of pyranose : furanose forms.
† $[\alpha]_D$ +119°. ‡ $[\alpha]_D$ +12°.

the individual components, although suitable separative methods were available if larger quantities of material had been produced. Measurement of the copper-reducing power of the mixture gave, however, an estimate of 1 : 4-linked sugars, the amount of 1 : 2- and 1 : 1-linked sugars being obtained by difference. [Trehaloses (1 : 1-linked) have no reducing group, while the 1 : 2-linked sugars, kojibiose [16] and sophorose, although possessing a free reducing group, do not reduce Somogyi copper reagent.[16, 20]]

The Table shows that the relative amounts of reversion products obtained when glucose is heated (for two hours) with (*a*) aqueous sulphuric acid alone and (*b*) formic acid followed by aqueous sulphuric acid, are considerably different. Thus the percentage yield of reversion products with (*b*) is 5 times that obtained with (*a*). This may possibly be related to the concentration of the glucose. In the first case the concentration of glucose in 0·33N-sulphuric acid was 1·0%. In the second case, the initial concentration of the glucose in 90% formic acid was 6%; its final concentration, after the addition of the aqueous sulphuric acid, was, however, only 0·4%. A striking feature is the large proportion of anhydroglucose formed in each case. With aqueous sulphuric acid, it constitutes 70% of the total reversion products and with formic acid, 50%. This is in contrast to the observations of Thompson *et al.*[8] that lævoglucosan (only the pyranose form was detected) is a relatively minor product of the reversion which occurs in 0·082N-hydrochloric acid. The concentration of glucose used by these authors was, however, 30% and it is to be expected that the higher the concentration of the sugar, the greater will be the tendency for inter-, rather than intra-, molecular condensation to occur.

In the group of disaccharide reversion products, the 1 : 6-linked sugars, isomaltose and gentiobiose, preponderate, whichever method of acid treatment is used. It is perhaps noteworthy that the 1 : 1- and 1 : 2-linked disaccharides together constitute 6% of the total reversion products produced by aqueous sulphuric acid whereas in the formic acid treatment these disaccharides constitute 18%.

The validity of the method of linkage analysis of a polysaccharide by partial acid hydrolysis is dependent upon the demonstration that the oligosaccharides formed are not products of reversion synthesis and this demonstration is not complete when the control experiments are concerned, as here, with reversion synthesis from the monosaccharide. The disaccharide reversion products from glucose are formed by reaction between the reducing group of one glucose molecule with a hydroxyl group of a second and obviously the concentration of reducing groups will be much less during the partial hydrolysis of a polyglucose than when the equivalent of glucose is being treated under the same conditions.

[16] Barker, Bourne, Grant, and Stacey, *Nature*, 1956, **178**, 1221; Haq and Whelan, *ibid.*, 1222.
[17] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[18] Haq and Whelan, *J.*, 1956, 4543.
[19] Dimler, *Adv. Carbohydrate Chem.*, 1952, **7**, 37.
[20] Somogyi, *J. Biol. Chem.*, 1945, **160**, 61.

XUM

In consequence, the amounts of disaccharides formed from glucose will exceed those formed by reversion during acid hydrolysis of the polysaccharides.

There is, however, another factor which would work in the opposite direction and increase the reversion tendency with the polysaccharide as against the monosaccharide. When a glycosidic linkage is severed by acid the two saccharide fragments may combine with water or, alternatively, combine with each other or with other fragments. In the latter case, the energy associated with the original linkage could be available to accelerate the formation of reversion products. An analogy exists in the case of enzymic synthesis of glucosidic linkages. The " transfer " reactions catalysed by, for example, phosphorylase or D-enzyme,[21] wherein linkage-scission precedes linkage-synthesis, occur much more rapidly than does the dimerisation of glucose by the agency of a glucosidase.[15]

There is, therefore, some uncertainty as to whether control experiments with a monosaccharide substrate provide a reliable guide to the true extent of acid reversion during polysaccharide hydrolysis, and it is clear that a disaccharide found in the partial acid hydrolysate of a polysaccharide can be regarded as a structural unit of the latter only if isolated in a yield many times as great as that obtained in the monosaccharide control experiments.

In conclusion it is suggested that a better method of providing control data for reversion products occurring during linkage analysis would be to study the formation of such substances from the disaccharide containing the main polymeric linkage of the polysaccharide, rather than from the monosaccharide; *i.e.*, in an investigation of laminarin, laminaribiose should be treated under the same conditions. In any case, reversion synthesis must be kept at a minimum by maintaining, so far as is practicable, minimal temperature and concentrations of polysaccharide [5] and acid during hydrolysis.

## Experimental

Evaporation was at 40° under diminished pressure, unless otherwise stated, and the pH was maintained at 5—6 by adjustment with sodium hydroxide or acetic acid. Optical rotation was measured in 4-dm. tubes.

*Test for Purity of Glucose.*—Anhydrous D-glucose (30 g.; B.D.H. " AnalaR " quality) was dissolved in water and adsorbed on charcoal–Celite which was eluted with water and then with 25% (v/v) ethanol as described below. The ethanolic eluate was evaporated to dryness and the residue dissolved in water (25 ml.). After treatment with Somogyi's deproteinising reagents [25] (total vol. 9 ml.), a 10 ml. portion of the solution was heated with 3N-sulphuric acid (10 ml.) at 100° for 3 hr. The reducing power (as glucose) was measured as described by Pirt and Whelan.[22] A second 10-ml. portion was treated in the same way but was not heated with the acid. When the reducing power of this solution was measured, 20 minutes' heating with copper reagent [20, 22] was necessary to allow full development of reducing power by disaccharides. The difference in reducing power between the hydrolysed and unhydrolysed solutions corresponded to the presence in the whole fraction of 36·8 mg. of disaccharide or 18·4 mg. of glucose anhydride (expressed in terms of glucose). That is, the " AnalaR " glucose was contaminated with 0·123% of disaccharide or 0·062% of glucose anhydride. Paper chromatography showed that the contaminants consisted largely of sugar anhydride with a little 1 : 6-linked disaccharide (isomaltose and/or gentiobiose). When assessing the amounts of reversion products (below) no correction was applied for the presence of these contaminants for the reason that they would be partly hydrolysed in the reversion reaction. Glucose disaccharides are about 25% hydrolysed during 2 hr. at 100° in 0·33N-sulphuric acid.

*Treatment of Glucose with 0·33N-Sulphuric Acid.*—A solution of chromatographically pure anhydrous D-glucose (30 g.) in 0·33N-sulphuric acid (3 l.) was heated in a boiling-water bath. Three experiments were performed, in which the heating times were 2, 5, and 10 hr., respectively. Each solution was then cooled quickly in running water, neutralised with 3N-sodium hydroxide, concentrated under reduced pressure to about 600 ml., and adsorbed on charcoal–Celite (100 × 4 cm.), prepared as described by Whelan *et al.*[9] Water (5 l.) was passed through

[21] Peat, Whelan, and Rees, *J.*, 1956, 44.
[22] Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224.

the column under pressure to remove salts and unchanged glucose. The reversion products were then eluted with 25% (v/v) aqueous ethanol (2·5 l.), and the solution evaporated to dryness. Inorganic matter and colloidal charcoal were removed by filtering a solution of the syrup in hot 80% (v/v) aqueous methanol through a " Sterimat " (GS grade).

*Successive Treatment of Glucose with 90% Formic Acid and 0·33N-Sulphuric Acid.*—" AnalaR " anhydrous D-glucose (21·3 g.) was heated, with mechanical stirring, in " AnalaR " 90% formic acid (342 ml.) at 98° for 25 min., more acid (114 ml.) was then added and heating continued for 15 min. The hot solution was then poured into hot 0·44N-sulphuric acid (4·56 l.) and heated for 1·5 hr. The cooled solution was neutralised with 6N-sodium hydroxide and concentrated until crystallisation began. The solution was then applied to charcoal–Celite (90 × 8·5 cm.) which was washed with water (13 l.) and then with 50% aqueous ethanol until all optically active material was desorbed. The ethanolic eluate was evaporated to dryness and freed from inorganic matter as described above.

*Fractionation of the Reversion Products.*—The weighed syrup was diluted with water to a concentration of about 160 mg./ml., and 80-mg. quantities (0·5 ml.) were applied to lines (46·5 cm. long) ruled parallel to the shorter sides of sheets of Whatman No. 3MM paper (18¼ × 22½ in.) which were irrigated in butan-1-ol–acetic acid–water (4 : 1 : 5, by vol.) until control strips showed a separation to have been achieved between lævoglucosan, the traces of glucose always present, and the reversion disaccharides. The papers were left to dry at room temperature for 24 hr. Thereafter guide strips (1·5 cm. wide) were cut from the sides and middle of the sheets and sprayed with silver nitrate–sodium hydroxide [17] to locate the three sugar zones. The disaccharide and lævoglucosan areas were then cut out from the unsprayed portions. Control experiments with a sample of 1 : 6-anhydro-β-D-glucofuranose, kindly supplied by Dr. R. J. Dimler, had shown the impossibility of locating this substance (which is not oxidised by periodate [18]) on a paper-chromatogram with spray reagents capable of locating non-reducing sugars. Since the anhydride fraction was likely to contain the pyranose as well as the furanose form, the whole of each chromatogram sheet from the bottom edge of the paper to the lower edge of the glucose zone was cut off; these portions of the papers were extracted together by being shaken with water (500 ml.) until the paper disintegrated, the mixture filtered, and the pulp twice more extracted with 250 ml. portions of water. The combined extracts were evaporated to dryness, the residue dissolved in hot 80% methanol, and the solution filtered and re-evaporated.

The sugar anhydride fraction was dissolved in water (50 ml.), and portions (3 ml.) removed for determination of sugar concentration after acidic hydrolysis to glucose.[22] The optical rotation of the anhydride fraction was measured and by using the $[\alpha]_D$ values of $-66{\cdot}3°$ [18] and $+42{\cdot}5°$ [19] quoted for 1 : 6-anhydro-β-D-glucose-pyranose and -furanose, respectively the proportion of the two forms present was calculated. The copper-reducing power of the fraction was also measured.[20] It was never more than 1·3% of that of glucose.

The disaccharide fraction, isolated in the same way, was dissolved in water (1 ml.), and applied to a line 46·5 cm. long, parallel to the shorter side of a sheet of Whatman No. 3MM paper (18¼ × 22½ in.) and about 7 in. from one end. The paper was supported horizontally in an apparatus [23] for ionophoresis in borate buffer, pH 8·7 (0·2M-boric acid + 0·05M-sodium borate; 2 : 3; v/v), the starting line being remote from the anode. A potential of 390 v was applied for 24 hr., after which the paper was dried at room temperature and guide strips removed for spraying with benzidine–trichloroacetic acid [24] (note that silver nitrate–sodium hydroxide does not react with sugars on alkaline borate-impregnated paper). Two zones were always detected, one of $M_G$ 0·6—0·7 containing 1 : 6- and 1 : 3-linked sugars, the other of $M_G$ 0·3 containing the remaining disaccharides. The unsprayed zones were cut out, with the inclusion of ample margins on either side of the sugar-areas. The sugars were then extracted with water (3 × 450 ml.), the paper pulp being filtered off between each extraction. To avoid alkaline decomposition, the pH was brought below 7, in the first extraction, by adding N-sulphuric acid. The salts were removed, and the sugars concentrated by passing the combined extracts through charcoal–Celite (20 × 2·5 cm.) which was washed with water until free from buffer and then eluted with 50% aqueous ethanol (200 ml.), this extract being finally evaporated to dryness.

[23] Latner, *Biochem. J.*, 1952, **51**, xii.
[24] Bacon and Edelman, *Biochem. J.*, 1951, **48**, 114.
[25] Somogyi, *J. Biol. Chem.*, 1945, **160**, 69.

XUM

The disaccharides of $M_G$ 0·3 were dissolved in water (10 ml.) and treated with Somogyi's deproteinising reagents [25] (4 ml.) to remove substances eluted from charcoal–Celite which interfere with cuprimetric determinations,[9] and 10 ml. of the centrifuged solution were diluted to 25 ml. The carbohydrate content was determined by acid hydrolysis and the reducing power (as maltose) was measured with Somogyi's reagent.

The disaccharides having $M_G$ 0·6—0·7 were freed from buffer salts as described above and refractionated, each on one sheet of Whatman No. 3MM paper in butan-1-ol–acetic acid–water, and the separated zones (1 : 6- and 1 : 3-linked sugars) located and extracted as before. The separated sugars were finally dissolved in 25 ml. of aqueous solution, their concentration measured by acid hydrolysis, and the optical rotation determined. On the assumption that these fractions were binary mixtures the amount of each component was calculated from the specific optical rotation, the following values of $[\alpha]_D$ for the pure substances being assumed: nigerose [26], +136°; laminaribiose [27], +18·6°; isomaltose [13], +122°; gentiobiose [15], +9·6°. A modification of the above method was used in the case of the disaccharides having $M_G$ 0·6—0·7 obtained in the formic acid–aqueous sulphuric acid treatment of glucose. After adsorption of the dissacharide on charcoal–Celite and removal of buffer, the column (75 × 3 cm.) was subjected to gradient elution,[28] a reservoir of water being connected to the column and the level maintained in the reservoir by feeding in 15% ethanol through a constant-head device. Fractions (100 ml.) were collected under diminished pressure and their optical rotation measured. Positive-rotating material was detected in fractions 22—30 which were combined and evaporated. A further six fractions were collected and combined with the eluate obtained on subsequently washing the column with 20% ethanol. This second fraction was then separated by paper chromatography as described above for the disaccharides with $M_G$ 0·6—0·7. In this way isomaltose (fractions 22—30) was separated from gentiobiose. The isomaltose fraction was treated with deproteinising reagents and its specific optical rotation calculated from the rotation of its solution and the sugar concentration as measured by acid hydrolysis (see Table). The same measurements were made on the gentiobiose and the mixed 1 : 3-disaccharide fractions, the solutions being first " deproteinised." This purification procedure was later found to be unnecessary for sugars eluted from paper and was reserved for products eluted from charcoal.

*Preparation and Analysis of Sugar Anhydrides.*—Glucose (30 g.) was heated at 100° in 90% formic acid (111 ml.) for 25 min., a further 37 ml. of acid were then added and the heating continued for 15 min. Sulphuric acid (0·44N; 1480 ml.) was added and heating at 100° was continued for 3 hr. The cooled solution was neutralised and the sugar anhydride fraction isolated by charcoal–Celite and paper chromatography as previously described. The product was taken up in water (100 ml.). The concentration of sugar anhydride was measured by acidic hydrolysis to glucose (2 hr. at 100°) and measurement of copper-reducing power by Pirt and Whelan's method.[22] Heating for a longer time (4 hr.) did not increase the reducing power. The yield of anhydride {$[\alpha]_D$ −41·4° (*c*, 0·18)} was 181 mg. and a portion equivalent to 3·62 mg. had no measurable copper-reducing power.[20] The volume of the remaining solution was reduced to one-third and the concentration redetermined (4·99 mg./ml.). A portion (5 ml.) was stored in the dark with 0·37M-sodium metaperiodate (10 ml.). The consumption of periodate was measured by adding a portion (1 ml.) to a solution of potassium iodide (0·5 g.) in 2N-sulphuric acid (5 ml.) and titrating the liberated iodine with 0·05N-sodium thiosulphate. Formic acid production was measured by mixing a 1 ml. portion with ethylene glycol (0·3 ml.) and after 10 min. adding potassium iodide (0·2 g.) and titrating with neutral 0·005N-thiosulphate. Measurements were made on the oxidation mixture and on a control containing water in place of sugar anhdride solution. The consumption of periodate was 1·56 mol. after 4 hr. and after 21·5 hr., and the amounts of formic acid liberated were 1·59 and 1·60 mol., respectively.

We thank the Department of Scientific and Industrial Research for the award of a maintenance grant (to T. E. E.) and the Agricultural Research Council for financial support.

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, July 25th*, 1957.]

[26] Barker, Bourne, and Stacey, *J.*, 1953, 3084.
[27] Bachli and Percival, *J.*, 1952, 1243.
[28] Alm, *Acta Chem. Scand.*, 1952, **6**, 1186.

## 115. *The Constitution of Larch ε-Galactan.*

By G. O. Aspinall, E. L. Hirst, and Else Ramstad.

Hydrolysis of methylated larch ε-galactan yields 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose, 2 : 3 : 4-tri-*O*-methyl-D-galactose, and 2 : 4-di-*O*-methyl-D-galactose in approximately equal quantities, together with smaller amounts of 2 : 3 : 4-tri-*O*-methyl-L-arabinose, 2 : 5-di-*O*-methyl-L-arabinose, 2 : 4 : 6-tri-*O*-methyl-D-galactose, and 2-*O*-methyl-D-galactose. Partial acid hydrolysis of the polysaccharide affords two disaccharides, 6-*O*-β-D-galactopyranosyl-D-galactose and 3-*O*-β-D-galactopyranosyl-D-galactose, and a series of higher oligosaccharides. Partial acid hydrolysis of the fragment remaining after degradation of the periodate-oxidised polysaccharide with phenylhydrazine affords 3-*O*-β-D-galactopyranosyl-D-galactose, and only small amounts of the second disaccharide. It is concluded (i) that the larch polysaccharide is a highly branched arabogalactan in which the majority of L-arabinose residues are accommodated as 3-*O*-β-L-arabopyranosyl-L-arabofuranosyl side-chains, and (ii) that the framework of the molecule consists of chains of 1 : 3-linked β-D-galactopyranose residues, the majority of which carry side-chains containing an average of two 1 : 6-linked β-D-galactopyranose residues.

It has been shown previously [1] that the water-soluble ε-galactan from European larch wood (*Larix decidua*) is a complex polysaccharide containing D-galactose and L-arabinose residues in the approximate ratio of 6 : 1. Evidence was presented which indicated that the material examined was a mixture, the main component being a galactan containing only minimal quantities of arabinose residues, and there also was present either an arabogalactan or an araban and a second galactan. Hydrolysis of the methylated polysaccharide derived from the main component gave equimolecular proportions of 2 : 3 : 4 : 6-tetra-, 2 : 3 : 4-tri-, and 2 : 4-di-*O*-methyl-D-galactose, indicating a highly branched molecule for which several possible repeating units could be suggested. More recently Jones [2] has isolated 3-*O*-β-L-arabopyranosyl-L-arabinose from the products of mild acid hydrolysis, indicating the presence in the polysaccharide of some arabinose residues in the less common pyranose form. We now report the results of a further investigation of this material.

ε-Galactan, isolated from larch sawdust by aqueous extraction, gave on hydrolysis galactose (85%) and arabinose (12%). No evidence of heterogeneity in this sample was found by Heidelberger [3] in a study of the precipitation reactions of the polysaccharide with various pneumococcal sera. Furthermore, an ultracentrifugal examination, kindly carried out by Dr. C. T. Greenwood, indicated the presence of only one molecular species. This latter result is in contrast to the findings of Mosimann and Svedberg,[4] whose ultracentrifugal measurements indicated the presence of two distinct components in the ε-galactan from European larch.

ε-Galactan was converted into its fully methylated derivative, but we could find no evidence of heterogeneity of the type encountered in the earlier investigation.[1] Hydrolysis of the methylated polysaccharide gave 2 : 3 : 4 : 6-tetra-, 2 : 3 : 4-tri-, and 2 : 4-di-*O*-methyl-D-galactose in approximately equimolecular proportions, together with smaller amounts of 2 : 3 : 4-tri- and 2 : 5-di-*O*-methyl-L-arabinose, and 2-*O*-methyl-D-galactose. Since the physical constants found for the tri-*O*-methyl-D-galactose did not correspond exactly to those of pure 2 : 3 : 4-tri-*O*-methyl-D-galactose, a search was made for other trimethyl ethers of galactose. Careful fractional crystallisation of the aniline derivatives afforded a small quantity of the aniline derivative of 2 : 4 : 6-tri-*O*-methyl-D-galactose. The proportions of the two trimethyl ethers were estimated by determining the formaldehyde formed on periodate oxidation of the derived hexitols; the 2 : 3 : 4-isomer yields

[1] Campbell, Hirst, and Jones, *J.*, 1948, 774.
[2] Jones, *J.*, 1953, 1672.
[3] Heidelberger, *J. Amer. Chem. Soc.*, 1955, **77**, 4308.
[4] Mosimann and Svedberg, *Kolloid Z.*, 1942, **100**, 1.

XUM

formaldehyde whereas the 2 : 4 : 6-isomer does not. The results indicated the presence in the mixture of 2 : 3 : 4- (92%) and 2 : 4 : 6-tri-*O*-methyl-D-galactose (8%). Since this work was completed Jones and Perry [5] have reported the use of a similar procedure for the estimation of the relative proportions of mixtures of methylated sugars.

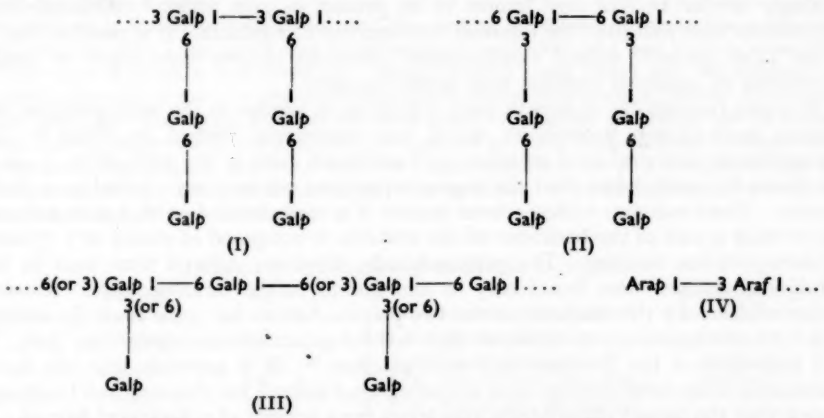
These results are in general accord with the previous findings [1] in respect of the main framework of galactose residues. The small quantity of galactose residues linked solely through $C_{(1)}$ and $C_{(3)}$ were not previously detected. Although the 2-*O*-methyl-D-galactose may have arisen from incomplete methylation of the polysaccharide, the absence of other monomethyl ethers of galactose suggests that this sugar may have structural significance, arising from a small proportion of doubly-branched galactose residues. 2 : 3 : 4-Tri-*O*-methyl-L-arabinose and 2 : 5-di-*O*-methyl-L-arabinose were isolated in approximately equimolecular amounts. In the absence of more than trace amounts of other arabinose derivatives it is clear that these sugars must represent fragments of an arabogalactan, and that on this evidence there is no indication of the presence in larch wood of polysaccharides composed solely of arabinose residues. Only traces of 2 : 3 : 5-tri-*O*-methylarabinose could be detected amongst the products of hydrolysis of the methylated polysaccharide and it is doubtful if terminal arabofuranose units are present to any significant extent in the polysaccharide. Since 3-*O*-β-L-arabopyranosyl-L-arabinose has been isolated from the products of partial acid hydrolysis of the polysaccharide,[2] it is now certain that the majority of arabinose residues are accommodated in 3-*O*-β-L-arabopyranosyl-L-arabofuranosyl side-chains, the furanose linkages being more easily cleaved on acid hydrolysis. Although this disaccharide has been isolated as an acid reversion from L-arabinose,[6] it is accompanied under these conditions by two other arabinose-containing disaccharides, neither of which was detected in the larch polysaccharide hydrolysate. Furthermore, in this instance, the disaccharide is destroyed when the hydrolysis is prolonged, whereas under the extreme conditions employed when acid reversion products are isolated in large amount [6] it is probable that an equilibrium is established between monomer and the various polymeric products.

On the basis of the methylation results various structures may be advanced for the repeating unit of the polysaccharide. Structures (I), (II), and (III) are representative of those containing an ordered arrangement of galactose residues; these structures do not take into account the mode of attachment of arabinose residues in side-chains (IV) to galactose. A partial distinction between the various possible structures has been made after the application of Barry's method of degradation [7] to the polysaccharide.

The periodate-oxidised ε-galactan was degraded by treatment with phenylhydrazine and acetic acid, and the products were separated into a mixture of compounds of low molecular weight and a polysaccharide residue. The products of low molecular weight were fractionated on alumina, and glyoxal bisphenylhydrazone and glycerosazone were isolated crystalline. Traces of galactosazone and arabinosazone were detected chromatographically, but the structural significance of these trace amounts is doubtful in view of the slightly acid conditions used in the degradation. Chromatography of the products of partial acid hydrolysis of the polysaccharide residue showed galactose, arabinose, and a series of galactose-containing oligosaccharides. The various structures represented by formula (III) can now be rejected since these contain only isolated galactose residues unattacked by periodate. The polysaccharide must contain, therefore, a resistant backbone of galactose residues with the majority of galactose residues, which are attacked by periodate, being accommodated in the side-chains of the molecular structure (I or II). A distinction between structures (I) and (II) has been made on the basis of evidence obtained from a study of the oligosaccharides isolated on partial acid hydrolysis of ε-galactan and of the periodate-oxidised polysaccharide after degradation with phenylhydrazine.

[5] Jones and Perry, *J. Amer. Chem. Soc.*, 1957, **79**, 2787.
[6] Ball, Jones, Nicholson, and Painter, *T.A.P.P.I.*, 1956, **39**, 438.
[7] Barry and Mitchell, *J.*, 1954, 4020.

The oligosaccharides derived from ε-galactan on partial hydrolysis were separated on charcoal–Celite by elution with water containing increasing quantities of ethanol. Two disaccharides, readily distinguishable by paper chromatography, were isolated pure. The 1 : 6-linked galactobiose was differentiated from the 1 : 3-linked isomer by the fact that the latter only gave formaldehyde on periodate oxidation. Galactobiose I had an optical rotation indicative of a β-linkage, and the structure of the disaccharide was established since hydrolysis of the methylated derivative afforded 2 : 3 : 4 : 6-tetra- and 2 : 3 : 4-tri-*O*-methyl-D-galactose. Galactobiose II, isolated crystalline, had similar physical constants to those recorded for 3-*O*-β-D-galactopyranosyl-D-galactose, isolated from the graded hydrolysis of *Acacia pycnantha* gum.[8] The mode of linkage in the disaccharide was confirmed by the isolation of 2 : 3 : 4 : 6-tetra- and 2 : 4 : 6-tri-*O*-methyl-D-




galactose on hydrolysis of the methylated derivative. Three galactose-containing trisaccharides were also isolated, and, although insufficient quantities of these compounds were available for full structural determinations, preliminary experiments provided evidence of their probable structures. Galactotriose I, isolated crystalline, gave only 6-*O*-galactosylgalactose and galactose on partial acid hydrolysis and is probably *O*-D-galactopyranosyl-(1 ⟶ 6)-*O*-D-galactopyranosyl-(1 ⟶ 6)-D-galactose. Galactotriose II gave both the 1 : 3- and the 1 : 6-linked galactobiose on partial hydrolysis, but since the derived glycitol gave galactose and no reducing disaccharide on partial hydrolysis, it is probable that the branched trisaccharide is 3 : 6-di-*O*-galactopyranosylgalactose. Galactotriose III gave 3-*O*-galactosylgalactose and galactose on partial hydrolysis and is probably *O*-galactopyranosyl-(1 ⟶ 3)-*O*-galactopyranosyl-(1 ⟶ 3)-galactose. Such a 1 : 3-linked galactotriose could only arise from a polysaccharide in which the repeating unit (I) is an important part of the molecular structure.

The degraded polysaccharide, remaining after treatment of the periodate-oxidised ε-galactan with phenylhydrazine and acetic acid, was subjected to graded acid hydrolysis, the products were fractionated on charcoal, and the disaccharide fractions were examined. 3-*O*-β-D-Galactopyranosyl-D-galactose, isolated crystalline, was the major component of this fraction and only small quantities of the 1 : 6-linked disaccharide were detected chromatographically. It follows from this observation that the backbone of the polysaccharide, resistant to attack by periodate, is composed of chains of 1 : 3-linked β-D-galactopyranose residues. The significance of the small amount of 6-*O*-galactosylgalactose detected in this experiment is not yet clear. It is possible that the backbone of the molecule may contain a small proportion of 1 : 6-linkages. Alternatively, if the arabinose containing side-chains are attached to the outer chains of the molecule, *e.g.*, through

[8] Hirst and Perlin, *J.*, 1954, 2622; Perlin, *Analyt. Chem.*, 1955, **27**, 396.

position 3 of galactose, some galactose residues in the outer part of the molecular structure would be unattacked by periodate and would give rise to the 1 : 6-linked disaccharide on partial hydrolysis of the degraded polysaccharide.

We can now summarise the main conclusions from these experiments. The ε-galactan from European larch is a highly branched arabogalactan in which the majority of arabinose residues are accommodated as 3-*O*-β-L-arabopyranosyl-L-arabofuranosyl side-chains (IV) linked to the framework of galactose residues. There is no evidence yet for the presence in larch wood of a polysaccharide composed solely of arabinose residues. The arrangement of galactose residues is best represented by the repeating unit (I), in which each D-galactopyranose residue in a 1 : 3-linked chain carried through position 6 an average of two 1 : 3-linked D-galactopyranose residues. In this respect, the molecular structure is strikingly similar to that now known to be present in gum arabic.[9] Although these experiments have indicated the essential homogeneity of ε-galactan, it is possible that, as in the xylan group,[10] several closely-related molecular species with larger or smaller proportions of arabinose residues may occur together.

In many respects the European larch ε-galactan is similar to the arabogalactan from Western larch (*Larix occidentalis*), which was extensively studied by White.[11] This polysaccharide also contained galactose and arabinose units in the ratio of 6 : 1, and it was shown by methylation that the D-galactopyranose residues were linked in a similar manner. There was also evidence from studies of a methylated degraded polysaccharide that at least a part of the backbone of the molecule is composed of chains of 1 : 3-linked D-galactopyranose residues. The polysaccharide, however, differed from ours in that L-arabinose residues were found only as end groups in the furanose form. Recently, further evidence for the similarity of the two polysaccharides has come from the isolation of 3-*O*-β-L-arabopyranosyl-L-arabinose and 6-*O*-β-D-galactopyranosylgalactose from the mild hydrolysis of the Western larch arabogalactan.[12] It is probable that the former disaccharide arises from cleavage of an arabofuranosyl linkage, but Bouveng and Lindberg [12] suggest that the second disaccharide also arises from scission of a furanosyl linkage. In preliminary experiments on the European larch ε-galactan it was shown that under the hydrolysis conditions required to release 3-*O*-arabopyranosylarabinose, appreciable quantities of the 1 : 6-linked galactobiose were also formed. Furthermore, attempts to prepare an arabinose-free galactan by selective hydrolysis under mild conditions failed as extensive breakdown of the polysaccharide to galactose-containing oligosaccharides occurred before all the arabinose residues were removed. Since we could find no evidence for the presence in the polysaccharide of galactofuranose residues, it is clear that in this case the rates of hydrolysis of arabofuranosides and galactopyranosides are not markedly different.

## Experimental

Paper chromatography was on Whatman No. 1 filter paper, the following solvent systems (v/v) being used: (A) butan-1-ol–ethanol–water (40 : 11 : 19); (B) ethyl acetate–pyridine–water (10 : 4 : 3); (C) benzene–ethanol–water (169 : 47 : 15; upper layer); (D) butan-1-ol–formic acid–water (500 : 115 : 385; upper layer); (E) butan-2-one saturated with water.

The larch ε-galactan was prepared at the Forest Products Research Laboratory, Princes Risborough, by extraction of the sawdust with water, purification by passage through columns of Amberlite resins IR-120 and IRA-400, and precipitation from aqueous solution with ethanol. The polysaccharide yielded on hydrolysis galactose (85%) and arabinose (12%), the proportions of the sugars being estimated by Hirst and Jones's [13] method. Preliminary chromatographic studies showed that when the ε-galactan was heated at 100° with 0·01N-hydrochloric acid,

[9] Dillon, O'Ceallachain, and O'Colla, *Proc. Roy. Irish Acad.*, 1953, **55**, *B*, 331; 1954, **57**, *B*, 31; Smith and Spriestersbach, Amer. Chem. Soc. Meeting, Minneapolis, Sept., 1955, Abs. Papers, 7D.
[10] Hirst, *J.*, 1955, 2974.
[11] White, *J. Amer. Chem. Soc.*, 1941, **63**, 2871; 1942, **64**, 302, 1507, 2838.
[12] Bouveng and Lindberg, *Acta Chem. Scand.*, 1956, **10**, 1515.
[13] Hirst and Jones, *J.*, 1949, 1659.

arabinose, galactose, 3-*O*-arabopyranosylarabinose, and galactobiose I were released. On prolonged hydrolysis the arabinose-containing disaccharide disappeared and there was no indication of its formation under these conditions as an acid reversion product. An attempt was made to prepare a degraded galactan devoid of arabinose residues by mild acid hydrolysis (0·01N-hydrochloric acid at 100°), but even after heating for 20 hr. the precipitable degraded polysaccharide still contained arabinose residues, and galactose and galactose-containing oligosaccharides could be detected in the supernatant liquid.

*Methylation of ε-Galactan.*—ε-Galactan was methylated extensively with methyl sulphate and sodium hydroxide to give a methylated polysaccharide, $[\alpha]_D^{18}$ −49° (*c* 1·2 in chloroform), $[\alpha]_D^{18}$ −27° (*c* 1·1 in methanol) [Found: OMe, 44·1; dimethylaraban, 5·2% (based on the yield of furfuraldehyde on distillation with 12% hydrochloric acid under standard conditions [14])]. Fractionation of the methylated polysaccharide failed to yield materials differing significantly in dimethylaraban content.

*Hydrolysis of Methylated ε-Galactan and Separation of Methylated Sugars.*—The methylated polysaccharide (10 g.) was suspended in 2N-sulphuric acid (150 ml.) and kept at room temperature until dissolution was complete. Water (150 ml.) was added and the solution was warmed slowly so that the methylated polysaccharide remained in solution and was then heated at 100° for 7 hr. The cooled solution was neutralised with barium carbonate and on concentration gave a syrupy mixture of methylated sugars (9·8 g.). A portion (5 g.) of the hydrolysate was separated on cellulose (80 × 3·5 cm.) with light petroleum (b. p. 100—120°)–butan-1-ol (7 : 3) saturated with water as eluant to give ten fractions; a further fraction was obtained by elution of the cellulose with water.

*Analysis of hydrolysate of methylated ε-galactan.*

| Fraction | Material eluted (g.) | $R_G$ in solvent A * | Paper chromatography sugar * | Sugar given after demethylation * |
|---|---|---|---|---|
| 1 | 0·006 | 0·96 | 2 : 3 : 5-trimethylarabinose | arabinose |
| 2 | 0·437 | 0·96 (*t*)<br>0·90 | 2 : 3 : 5-trimethylarabinose<br>2 : 3 : 4 : 6-tetramethylgalactose | arabinose (*t*)<br>galactose |
| 3 | 0·701 | 0·90 | 2 : 3 : 4 : 6-tetramethylgalactose | — |
| 4 | 0·033 | 0·90<br>0·86<br>0·83 | 2 : 3 : 4 : 6-tetramethylgalactose<br>2 : 5-dimethylarabinose<br>2 : 3 : 4-trimethylarabinose | —<br>—<br>— |
| 5 | 0·211 | 0·86<br>0·83 | 2 : 5-dimethylarabinose<br>2 : 3 : 4-trimethylarabinose | arabinose |
| 6 | 0·022 | 0·86<br>0·83<br>0·72 | 2 : 5-dimethylarabinose<br>2 : 3 : 4-trimethylarabinose<br>trimethylgalactose | arabinose<br>galactose |
| 7 | 0·970 | 0·72 | trimethylgalactose | galactose |
| 8 | 0·057 | 0·72<br>0·59 (*t*)<br>0·52 (*t*) | trimethylgalactose<br>unknown sugar<br>unknown sugar | galactose<br>arabinose (*t*) |
| 9 | 1·315 | 0·46 | 2 : 4-dimethylgalactose | — |
| 10 | 0·260 | 0·30 | 2-methylgalactose | — |
| 11 | 0·101 | — | galactose (*t*), arabinose (*t*) + methylated uronic acid | — |

* *t* = trace

*Identification of Sugars from Hydrolysis of Methylated ε-Galactan.*—*Fraction* 2. The syrup consisted almost entirely of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose, paper chromatography indicating only a trace of tri-*O*-methylarabinose. The syrup crystallised on nucleation and after recrystallisation from ether–light petroleum had m. p. and mixed m. p. 68° (Found: OMe, 52·5. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). The sugar was further characterised as 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-galactosylamine, m. p. and mixed m. p. 192°.

*Fraction* 3. The sugar, after recrystallisation, had m. p. and mixed m. p. (with 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose) 68°, $[\alpha]_D^{19}$ +142° (5 min.) ⟶ +117° (3 hr., const.) (*c* 1·1 in water)

[14] Dorée, "The Methods of Cellulose Chemistry," Chapman and Hall, London, 1947; Bott and Hirst, *J.*, 1932, 2621.

(Found: OMe, 53·1. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%), and its identity was confirmed by conversion into the aniline derivative, m. p. and mixed m. p. 192°.

*Fraction* 5. The syrup had OMe, 41·0%, $[\alpha]_D^{20}$ +82° (*c* 1·2 in water), and chromatography showed two components travelling at the same rates as 2 : 3 : 4-tri-*O*-methyl and 2 : 5-di-*O*-methyl-L-arabinose, with traces of methylated galactoses. The mixture of sugars (270 mg.), obtained from a separate experiment, was separated on filter sheets, solvent C being used, to give fractions 5*a* (111 mg.) and 5*b* (154 mg.), each of which contained only traces of the second component. Fraction 5*a*, $[\alpha]_D^{20}$ +120° (*c* 2·2 in water) (Found: OMe, 46·1. Calc. for $C_9H_{16}O_5$: OMe, 48·4%), was identified by conversion into 2 : 3 : 4-tri-*O*-methyl-L-arabonophenylhydrazide, m. p. 157° (Jones [2] quotes m. p. 159°). Fraction 5*b*, $[\alpha]_D^{18}$ −3° (*c* 1·5 in water) (Found: OMe, 33·9. Calc. for $C_7H_{14}O_5$: OMe, 34·8%), was identified by conversion into 2 : 5-di-*O*-methyl-L-arabonomide, m. p. 131°.

*Fractions* 4 *and* 6. The combined fractions were shown by chromatography to contain the same two sugars as fraction 5, together with smaller quantities of methylated galactoses. A portion (41 mg.), separated on filter sheets by using solvent C, yielded chromatographically pure 2 : 3 : 4-tri-*O*-methyl- (11 mg.) and 2 : 5-di-*O*-methyl-arabinose (22 mg.).

*Fraction* 7. The crystalline sample, which travelled on the chromatogram at the same rate as 2 : 3 : 4- and/or 2 : 4 : 6-tri-*O*-methyl-D-galactose, had $[\alpha]_D^{20}$ +125° (5 min.) ⟶ +104° (2 hr., const.) (*c* 1·1 in water) and after dehydration at 60° over phosphoric oxide under reduced pressure had $[\alpha]_D^{20}$ +109° (equil.) (*c* 1·1 in water) [Found (after dehydration): OMe, 41·3. Calc. for $C_9H_{18}O_6$: OMe, 41·9%]. Recrystallisation from acetone–ether–light petroleum gave a substance, m. p. (unaltered on further recrystallisation) 56°, $[\alpha]_D^{20}$ +139° (5 min.) ⟶ +109° (2 hr., const.) (*c* 1·1 in water) (Found: OMe, 38·2. Calc. for $C_9H_{18}O_6,H_2O$: OMe, 38·7%). {2 : 3 : 4-Tri-*O*-methyl-D-galactose monohydrate is reported to have m. p. 80°, $[\alpha]_D$ +152° ⟶ +114° (in water) and 2 : 4 : 6-tri-*O*-methyl-D-galactose to have m. p. 104—105°, $[\alpha]_D$ +124° ⟶ +93° (in water).} A sample (100 mg.) was dehydrated and refluxed with ethanolic aniline for 5 hr.; recrystallisation of the product from acetone yielded the characteristic plates of 2 : 3 : 4-tri-*O*-methyl-*N*-phenyl-D-galactosylamine, m. p. and mixed m. p. 166° (a mixture with the characteristic needles of 2 : 4 : 6-tri-*O*-methyl-*N*-phenyl-D-galactosylamine, m. p. 171°, had m. p. 144°). Concentration of the mother liquor yielded a mixture, m. p. 143°, of needles and plates but it was not possible to separate the two components.

*Fraction* 9. The chromatographically pure sugar was recrystallised from acetone containing 1% of water and had m. p. and mixed m. p. (with 2 : 4-di-*O*-methyl-D-galactose monohydrate) 102°, $[\alpha]_D^{20}$ +136° (5 min.) ⟶ +86° (2 hr., const.) (*c* 1·1 in water) (Found: OMe, 27·1. Calc. for $C_9H_{18}O_6,H_2O$: OMe, 27·2%). The identity of the sugar was confirmed by conversion into 2 : 4-di-*O*-methyl-*N*-phenyl-D-galactosylamine, m. p. and mixed m. p. 215°.

*Fraction* 10. The sugar (recrystallised from glacial acetic acid) had m. p. and mixed m. p. (with 2-*O*-methyl-D-galactose) 148—149°, $[\alpha]_D^{20}$ +53° (5 min.) ⟶ +85° (2 hr., const.) (*c* 0·9 in water), and the derived 2-*O*-methyl-*N*-phenyl-D-galactosylamine had m. p. 163°.

*Fraction* 11. The main component behaved chromatographically as a methylated uronic acid with low mobility in neutral solvents but having $R_G$ 0·84 in solvent D and giving a characteristic cherry-red colour with aniline oxalate.

*Re-examination of Tri-O-methylgalactose Fraction.*—Recrystallisation of the tri-*O*-methylgalactose fraction (from a separate experiment) from acetone–light petroleum afforded 2 : 3 : 4-tri-*O*-methyl-D-galactose hydrate, m. p. 73—76° (some sintering from 65°). Tri-*O*-methylgalactose (0·6 g.; anhydrous) was heated with aniline (0·3 ml.) in ethanol (20 ml.) for 1 hr. After removal of solvent the crystalline product was fractionally crystallised from acetone and acetone–light petroleum. The first fractions were composed solely of the aniline derivative (plates), m. p. and mixed m. p. 163—165°, of 2 : 3 : 4-tri-*O*-methyl-D-galactose. Subsequent fractions contained two crystalline forms and mechanical separation of the needles, followed by two recrystallisations from acetone–light petroleum, afforded the aniline derivative (needles), m. p. 166—167°, mixed m. p. (with sample, m. p. 178°) 169—171°, of 2 : 4 : 6-tri-*O*-methyl-D-galactose ; the m. p. was depressed on admixture with the aniline derivative of 2 : 3 : 4-tri-*O*-methyl-D-galactose.

*Estimation of the Relative Proportions of Tri-O-methylgalactoses.*—Methyl ethers of D-galactose were converted into the corresponding methyl ethers of D-galactitol. The sugar (200 mg.) in water (10 ml.) was added to potassium borohydride (60 mg.) in water (5 ml.). The solution stood for 14 hr. at room temperature, excess of borohydride was destroyed by the

addition of acetic acid, the solution was de-ionised by passage through columns of ion-exchange resins, Amberlite IRA-400 and Zeo-Karb 225, and concentrated to a crystalline residue. These materials were used without further purification in the periodate oxidation experiments. 2 : 4-Di-*O*-methyl-D-galactose afforded 2 : 4-*di*-O-*methyl*-D-*galactitol*, which after recrystallisation from ethanol–light petroleum had m. p. 133—134°, $[\alpha]_D^{20}$ +16° (*c* 0·3 in water) (Found: OMe, 30·1. $C_8H_{18}O_6$ requires OMe, 29·5%). The mixture of tri-*O*-methylgalactoses afforded the corresponding mixture of galactitols, recrystallisation from ethanol–light petroleum giving 2 : 3 : 4-*tri*-O-*methyl*-D-*galactitol*, m. p. 119°, $[\alpha]_D^{20}$ +6° (*c* 0·8 in water) (Found: OMe, 42·0. $C_9H_{20}O_6$ requires OMe, 41·5%).

The formaldehyde formed on periodate oxidation of the methylated hexitols was determined with chromotropic acid by O'Dea and Gibbons's method.[15] 2 : 4-Di-*O*-methyl-D-galactitol gave theoretical amounts of formaldehyde (cf. D-glucose). The formaldehyde formed on oxidation of the mixture of tri-*O*-methyl-D-galactitols corresponded to the presence therein of 92% of the 2 : 3 : 4-isomer, and, by difference, of 8% of the 2 : 4 : 6-isomer.

*Degradation of Periodate-oxidised ε-Galactan with Phenylhydrazine.*—The polysaccharide (1·7 g.) was oxidised with sodium metaperiodate solution (120 ml.; 0·2M) for 144 hr. (consumption of periodate was complete, corresponding to the uptake of 8·7 moles of periodate per 6 residues of galactose and 1 residue of arabinose). The solution was treated with lead acetate to remove iodate and periodate, and then with dilute sulphuric acid to precipitate excess of lead. The solution of oxygalactan (160 ml.) was treated with phenylhydrazine (3·5 ml.) in 10% acetic acid (10 ml.), and the precipitate was washed with water and dried to a yellow powder (1·5 g.). The oxygalactan phenylhydrazine derivative was suspended in ethanol (40 ml.), phenylhydrazine (5 ml.) in glacial acetic acid (8 ml.) and water (15 ml.) was added, and the mixture was refluxed for 4 hr. Removal of the ethanol under reduced pressure yielded crystals A (1·7 g.) which were separated and washed. The filtrate was extracted with benzene and ether to give a dark red solution B, and concentration of the aqueous solution yielded a red gum C (0·6 g.).

The crystalline precipitate A was dissolved in benzene and adsorbed on alumina (80 g.). Elution with benzene (250 ml.) gave fraction Ai (1·0 g.) which on recrystallisation from benzene yielded glyoxal bisphenylhydrazone, m. p. and mixed m. p. 168°. Elution with 1 : 1 benzene–ether (350 ml.) gave fraction Aii (0·1 g.), recrystallisation from benzene yielding first *N*-acetylphenylhydrazine, m. p. and mixed m. p. 128°, and then glycerosazone, m. p. and mixed m. p. 130°. Elution with ether (175 ml.) gave fraction Aiii (0·25 g.), which on recrystallisation from benzene yielded *N*-acetylphenylhydrazine. Elution with 9 : 1 ethanol–water gave fractions Aiv (0·3 g.) (containing *N*-acetylphenylhydrazine), Av (0·04 g.), and Avi (0·01 g.). Circular-paper chromatography showed fraction Av to contain glycerosazone and a trace of galactosazone, and fraction Avi to contain glycerosazone, arabinosazone, and galactosazone.

The benzene and ether extracts (B) yielded more *N*-acetylphenylhydrazine on concentration (fraction Bi). The residual syrup was dissolved in benzene and adsorbed on alumina (100 g.). Elution with ether (500 ml.) yielded fraction Bii (0·05 g.), shown by chromatography to contain only glyoxal bisphenylhydrazone. Elution with 9 : 1 ethanol–water gave fractions Biii (1·06 g.) and Biv (0·07 g.). Fraction Biii on recrystallisation from benzene–light petroleum yielded *N*-acetylphenylhydrazine and chromatographic examination of the mother liquor showed glyoxal bisphenylhydrazone and glycerosazone. Chromatographic examination of fraction Biv showed arabinosazone, galactosazone, and material which did not move on the chromatogram. Hydrolysis of fraction Biv yielded galactose and arabinose.

The red gum (C) consisted of the backbone of the polysaccharide remaining unattacked by periodate, hydrolysis of which gave arabinose and galactose. Partial acid hydrolysis yielded a series of galactose-containing oligosaccharides.

*Partial Acid Hydrolysis of ε-Galactan.*—ε-Galactan (10 g.) was heated (boiling-water bath) in 0·2N-sulphuric acid for 3 hr. The cooled solution was neutralised with Amberlite resin IR-4B, concentrated to 100 ml., and poured into ethanol (400 ml.). The precipitated degraded polysaccharide was separated at the centrifuge and concentration of the supernatant liquid gave a syrup (D) (4·46 g.). The degraded polysaccharide was re-hydrolysed by N-sulphuric acid (200 ml.) for 1 hr. at 100° and gave syrup (E) (3·76 g.) and a gum (1·8 g.) insoluble in ethanol–water (4 : 1). Chromatography showed that syrups (D) and (E) contained similar mixtures of galactose, arabinose, and a series of oligosaccharides. The combined syrups (8·21 g.) were

[15] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.

XUM

dissolved in water and poured on charcoal–Celite (1 : 1; 300 g.). Elution with water gave fraction 1 (6·12 g.) containing galactose and arabinose. Elution with water containing 2·5% of ethanol gave fraction 2 (368 mg.) containing a disaccharide (galactobiose I), $R_{Gal}$ 0·40 in solvent B, and traces of other sugars. Elution with water containing 5% of ethanol gave fraction 3 (260 mg.) containing a disaccharide (galactobiose II), $R_{Gal}$ 0·60 in solvent B. Elution with water containing 7·5% of ethanol gave fraction 4 (40 mg.), containing an oligosaccharide having $R_{Gal}$ 0·18 and traces of other sugars, and fraction 5 (160 mg.), having a major component with $R_{Gal}$ 0·25. Elution with water containing 10% of ethanol gave several small fractions (total, 58 mg.) containing mixtures of oligosaccharides having $R_{Gal}$ 0·25, 0·15, and 0·10, which were not examined. Elution with water containing 15% of ethanol gave fraction 6 (128 mg.), having a major component with $R_{Gal}$ 0·30.

*Examination of Oligosaccharides.—Fraction* 2. Chromatographically pure galactobiose I was isolated by separation on filter sheets with solvent B; the syrup had $[\alpha]_D^{17}$ +41° (*c* 1·18 in water). Oxidation of the disaccharide (12 mg.) with periodate [16] gave no formaldehyde. The major portion of the syrup (247 mg.) was dissolved in water (5 ml.), and methyl sulphate (1 ml.) and sodium hydroxide (1·5 ml., 30%) were added dropwise during 2 hr. Two more additions of methyl sulphate (7 ml.) and sodium hydroxide (10 ml., 30%) were made during a period of 6 hr. The reaction was completed by heating the solution on the boiling-water bath for 30 min., and the methylated disaccharide (243 mg.) was isolated by continuous extraction with chloroform for 12 hr. Hydrolysis of a sample (1 mg.) of the methylated disaccharide gave only tetra- and tri-*O*-methylgalactose. Methylated galactobiose I (93 mg.) was heated with N-hydrochloric acid (10 ml.) at 100° for 4 hr., and, after neutralisation with silver carbonate, gave a syrup (68 mg.) which was separated on a filter sheet with solvent E yielding fractions *a* (32 mg.) and *b* (25 mg.). Fraction *a* was characterised as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose and fraction *b* as 2 : 3 : 4-tri-*O*-methyl-D-galactose by conversion into the aniline derivatives, m. p. and mixed m. p. 192—193°, and m. p. 159—160° and mixed m. p. (with sample of m. p. 163—165°), 160—163° respectively.

*Fraction* 3. Galactobiose II crystallised readily and after recrystallisation from ethanol–water had m. p. 175—177°, $[\alpha]_D^{17}$ +78° (10 min.) ⟶ +63° (120 min., equil.) (*c* 0·67 in water). Hirst and Perlin [8] record m. p. 159—160°, $[\alpha]_D$ +62° (in water) for 3-*O*-β-D-galactopyranosyl-D-galactose monohydrate. Periodate oxidation [16] of a sample (12 mg.) gave formaldehyde, identified as the dimedone compound, m. p. 188—190°. Galactobiose II (100 mg.) was methylated as described above to give the methylated disaccharide (106 mg.). Hydrolysis of methylated galactobiose II (106 mg.) with N-hydrochloric at 100° for 4 hr., followed by neutralisation with silver carbonate, gave a syrup (75 mg.) which was separated on a filter sheet with solvent E yielding fractions *c* (34 mg.), *d* (25 mg.), and *e* (7 mg.). Fraction *c* was identified as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose and fraction *d* as 2 : 4 : 6-tri-*O*-methyl-D-galactose by conversion into the aniline derivatives, m. p. and mixed m. p. 185—187°, and m. p. and mixed m. p. 168—169°, respectively. Fraction *e* contained di-*O*-methylgalactose, probably arising from incomplete methylation of the disaccharide.

*Fraction* 4. A chromatographically pure sugar, having $R_{Gal}$ 0·18 in solvent B, m. p. 157—160°, $[\alpha]_D^{18}$ +16° (equil.) (*c* 0·38 in water), crystallised from ethanol–water. Partial acid hydrolysis of the sugar gave galactose, galactobiose I, and unchanged sugar.

*Fraction* 5. A sample of the major component, $R_{Gal}$ 0·25 in solvent B, was separated. The sugar gave on partial acid hydrolysis galactose, galactobiose I, galactobiose II, and unchanged sugar. Partial hydrolysis of the derived glycitol (borohydride reduction) gave galactose and no other reducing sugars.

*Fraction* 6. A sample of the major component, $R_{Gal}$ 0·30 in solvent B, was separated chromatographically. Partial acid hydrolysis of the sugar gave galactose, galactobiose II, and unchanged sugar, and partial hydrolysis of the derived glycitol gave galactose and galactobiose II.

*Partial Acid Hydrolysis of Gum* (C).—Gum (C), prepared from ε-galactan (6·5 g.) by phenylhydrazine degradation of the periodate-oxidised polysaccharide as described above, was heated with N-sulphuric acid (100 ml.) at 100° for 1 hr. The cooled solution was neutralised with Amberlite resin IR-4B and extracted with ether, the extract concentrated, and ethanol (2 vol.) added. A small precipitate was removed at the centrifuge and concentration of the supernatant liquid gave a syrup (1·82 g.) which was dissolved in water and poured on charcoal–

[16] Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476.

Celite (1 : 1; 100 g.). Elution with water gave a mixture (0·80 g.) of galactose and arabinose. Elution with water containing 2·5% of ethanol gave a syrup (33 mg.) containing galactose, arabinose, and a small amount of galactobiose I, $R_{Gal}$ 0·40. Elution with water containing 5% of ethanol gave the crystalline galactobiose II (60 mg.), $R_{Gal}$ 0·60, which after recrystallisation from ethanol–water had m. p. 176—179° and mixed m. p. 175—178°, $[\alpha]_D^{18}$ +78° (5 min.) ⟶ +62° (60 min., equil.) (*c* 0·51 in water).

The authors thank the Norwegian Council for Science and The Humanities (Norges Almenvitenskapelige Forskingsråd) for the award of a maintenance grant to one of them (E. R.) and the Rockefeller Foundation and Imperial Chemical Industries Limited for grants.

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF EDINBURGH. [*Received, September 16th*, 1957.]

---

## 116. *Immunopolysaccharides. Part VIII.* Enzymic Synthesis of* 6-O-α-D-*Glucopyranosyl*-3-O-*methyl*-D-*glucose by* Betacoccus arabinosaceous.

By S. A. BARKER, E. J. BOURNE, P. M. GRANT, and M. STACEY.

Examination of the homologous series of oligosaccharides produced by *B. arabinosaceous* (Birmingham) in a medium containing sucrose and 3-*O*-methyl-D-glucose has shown that they are formed by successive addition of glucosyl units in α-1 : 6-linkage to 3-*O*-methyl-D-glucose. This observation is of interest in connection with the mechanism of synthesis of the methylated polysaccharides which have been found in Nature.

THERE is now ample evidence,[1] that when *B. arabinosaceous* is grown on media containing sucrose and certain simple sugars the dextransucrase present can utilise the sucrose as its substrate and each added sugar as a receptor in the production of oligosaccharides. The structures of some of these oligosaccharides have already been reported.[1,2,3] The present investigation, in which 3-*O*-methyl-D-glucose was used as a receptor molecule, was of interest because the organism was known to synthesise a dextran containing α-1 : 3-linkages [4] and because of the known occurrence of 3-*O*-methyl-sugars in Nature (*e.g.*, 3-*O*-methyl-D-galactose [5] has been isolated from the hydrolysis products of slippery elm mucilage).

Chromatographically pure di-, tri-, and tetra-saccharides were isolated from a culture of *B. arabinosaceous* grown on a mineral medium containing sucrose (2%) and 3-*O*-methyl-D-glucose (10%). Of the glucose available from the sucrose, 20% was converted into disaccharide, 8% into trisaccharide, and 4% into tetrasaccharide.

The approximate molecular size of the disaccharide was ascertained by oxidation with alkaline hypoiodite [6] and by ionophoresis of its *N*-benzylglycosylammonium ion [7] in formate buffer (pH 1·8). The presence of one methoxyl group in the disaccharide was confirmed by a methoxyl determination.[8] Acidic hydrolysis yielded components identical with glucose and 3-*O*-methylglucose on paper chromatography and ionophoresis.

An α-glycosidic linkage in the disaccharide was indicated by (*a*) the relatively high specific rotation (+121° equil.), (*b*) its resistance to almond β-glycosidase, and (*c*) the presence of infrared absorption [9] at 837 cm.$^{-1}$ (α-linkages) and its absence from 890 cm.$^{-1}$.

* Part VII, *J.*, 1957, 3536.


1 Bailey, Barker, Bourne, and Stacey, *Nature*, 1955, **175**, 635; *J.*, 1957, 3536.
2 *Idem*, *Nature*, 1955, **176**, 1164.
3 Barker, Bourne, Grant, and Stacey, *Nature*, 1956, **178**, 1221.
4 Barker, Bourne, Bruce, Neely, and Stacey, *J.*, 1954, 2395.
5 Hirst, Hough, and Jones, *Nature*, 1950, **165**, 34; *J.*, 1951, 323.
6 *Idem*, *J.*, 1949, 928.
7 Barker, Bourne, Grant, and Stacey, *Nature*, 1956, **177**, 1125.
8 Belcher, Fildes, and Nutten, *Analyt. Chim. Acta*, 1955, **33**, 16.
9 Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.

The high mobility of its borate complex [10] on ionophoresis was indicative of a 1 : 6- or 1 : 3-glycosidic linkage.

The disaccharide consumed 2·97 mol. of periodate and produced 1·0 mol. of formic acid, but no formaldehyde. These values do not correspond to any of the theoretical values for 3-*O*-methylglucosylglucose structures containing a 1 : 2-, 1 : 3-, 1 : 4-, or 1 : 6-glycosidic linkage. Of the various glucosyl-3-*O*-methylglucose structures the only candidates are those containing a 1 : 4 or 1 : 6-glycosidic linkage. The possibility of the former was excluded by the relatively high $M_G$ value [10] of the disaccharide and by its ability to form a methyl furanoside. The assignment of the structure 6-*O*-α-D-glucopyranosyl-3-*O*-methyl-D-glucose to the disaccharide was confirmed by periodate oxidation of the methyl furanoside which consumed 1·8 mol. of periodate and produced 0·75 mol. of formic acid (theor.: 2 mol. of periodate, 1 mol. of formic acid). Hydrolysis of the periodate-oxidised methyl furanoside produced a component which moved similarly to 3-*O*-methylglucose on paper chromatographic and ionophoretic examination. Since 6-*O*-methylglucose resembles 3-*O*-methylglucose in its behaviour on paper chromatograms and paper ionophoretograms the above evidence is consistent with the disaccharide's being 3-*O*-α-D-glucopyranosyl-6-*O*-methylglucose, but this structure would involve transmethylation and is considered to be unlikely.

The molecular sizes of the trisaccharide and the tetrasaccharide were proved as for the disaccharide, and again total acidic hydrolysis gave only glucose and 3-*O*-methylglucose and the presence of one methoxyl group was confirmed as before. The products of partial acidic hydrolysis were in conformity with the structures *O*-α-D-glucopyranosyl-(1→6)-*O*-α-D-glucopyranosyl-(1→6)-3-*O*-methyl-D-glucose and *O*-α-D-glucopyranosyl-(1→6)-*O*-α-D-glucopyranosyl-(1→6)-*O*-α-D-glucopyranosyl-(1→6)-3-*O*-methyl-D-glucose.

The presence of α-linkages in both tri- and tetra-saccharide was confirmed by methods (*a*—*c*) above. The high mobilities of their borate complexes [10] were additional confirmation of 1 : 6-glycosidic linkages to their reducing units. Further evidence for the structure of the trisaccharide was obtained when it consumed 4·8 mol. of periodate with the production of 1·8 mol. of formic acid and no formaldehyde (theor.: 5, 2, 0 respectively).

The structures of the di-, tri- and tetra-saccharide therefore appear to conform with their formation by successive addition of glucosyl units in α-1 : 6-linkage to 3-*O*-methyl-D-glucose, also with previous studies where glucose and methyl α-D-glucoside were used as glucosyl acceptors.

## Experimental

*Synthesis and Separation of the Oligosaccharides.*—An aqueous medium (70 ml.) containing yeast extract (1%), $Na_2NH_4PO_4$ (0·5%), $KH_2PO_4$ (0·2%), $MgSO_4.7H_2O$ (0·05%), sucrose (2%), and 3-*O*-methyl-D-glucose (10%) was adjusted to pH 7 with sodium hydroxide and steam-sterilised at 15 lb./sq. in. for 30 min. This was then inoculated with *A. arabinosaceous* (Birmingham) and incubated at 25° for 3 days during which the pH fell to 4·6. After addition of ethanol (70 ml.), filtration, neutralisation, and removal of the ethanol, the residual solution was passed down a charcoal–" Celite " column [11] (l, 60 cm.; diam. 8 cm.). Washing with water eluted the monosaccharides and salts which were discarded. Gradient elution (0 → 20% aqueous ethanol) then gave a mixed disaccharide fraction (375 mg.) [illegible] chromatographically pure trisaccharide (84 mg.) and tetrasaccharide (41·4 mg.) fractions. A small amount (20 mg.) of higher oligosaccharides was also obtained. Refractionation of the mixed disaccharide fraction on a charcoal–" Celite " column removed a ketose-containing disaccharide, which reacted with naphtharesorcinol,[12] and left a disaccharide (290 mg.) which showed a single component on paper chromatography.

*Characterisation of the Disaccharide.*—(i) The *disaccharide* (Found: OMe, 8·1. $C_{12}H_{21}O_{10}$·OMe

[10] Foster, *J.*, 1953, 982.
[11] Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677.
[12] Lindberg and Wickberg, *Acta Chem. Scand.*, 1954, **8**, 569.
[13] Forsyth, *Nature*, 1948, **161**, 239.

requires OMe, 8·7%) showed infrared absorption peaks at 968, 921, 863, 837, and 767 cm.$^{-1}$ in the range 700—1000 cm.$^{-1}$. It gave <0·5% ash and had $[\alpha]_D^{20}$ +121° (equil.) (*c* 0·915 in $H_2O$).

(ii) *Paper chromatography and ionophoresis.* On a paper chromatogram irrigated with the organic phase of a butanol–ethanol–water–ammonia mixture (40 : 10 : 49 : 1) the disaccharide moved as a single component with $R_{Glucose}$ 0·65. When separated as its benzylamine derivative [14] in the same solvent it had $R_{Glucose}$ 0·77. On paper ionophoresis [10] in borate buffer (pH 10) the mobility of the disaccharide was 0·54. When separated as its *N*-benzylglycosylammonium ion [7] in an electrolyte of sodium hydroxide–formic acid (pH 1·8), the mobility (*M*) was 0·70.

(iii) *Oxidation with hypoiodite.* The disaccharide (4·3 mg.), on oxidation with alkaline hypoiodite,[6] consumed iodine equivalent to 2·0 mg. of glucose (92% of the theoretical value for a glucosyl-mono-*O*-methylglucose).

(iv) *Hydrolysis.* The disaccharide (5 mg.) was heated with 1·5N-sulphuric acid (3 ml.) at 100° for 4 hr. Paper chromatography and ionophoresis of the neutralised hydrolysate indicated the presence of glucose and 3-*O*-methyl-D-glucose.

The disaccharide (5 mg.) was incubated at 37° with almond emulsin [20 mg. in 0·05M-acetate buffer (3 ml., pH 5)]. Paper chromatography of the digest after incubation for 3 days indicated only negligible hydrolysis to glucose and 3-*O*-methylglucose while controls containing cellobiose, lactose, or laminaribiose showed complete hydrolysis after the same time.

(v) *Periodate oxidation.* The disaccharide (76·2 mg.) was oxidised with 0·075M-sodium periodate (50 ml.) at 18°. The periodate consumption, expressed in moles per mole of disaccharide, was: 1·18 (0·5 hr.), 2·30 (1·0 hr.), 2·46 (3 hr.), 2·97 (24 hr.), and 2·97 (36 hr.). After 36 hr., 1·0 mole of formic acid, but no formaldehyde, had been produced per mole of disaccharide.

The disaccharide (1·2 mg.) was dissolved in 4% methanolic hydrogen chloride (4·8 ml.) and [illegible] at room temperature. It showed $[\alpha]_D^{20}$ +54° (5 min.) ⟶ +34° (45 min., equil.). After 45 min. the solution was filtered, neutralised with silver carbonate (*ca.* 2 g.), filtered, concentrated *in vacuo*, and then freeze-dried (61·2 mg.); $[\alpha]_D^{20}$ was +45·7° (*c* 1·0 in $H_2O$). This methyl furanoside (35·4 mg.) was oxidised with 0·02M-sodium periodate (25 ml.) at 18°. The periodate consumed, expressed in moles per mole of methylfuranoside, was: 0·70 (45 min.), 1·06 (3 hr.), 1·60 (24 hr.), 1·80 (72 hr.). After 72 hr., 0·75 mole of formic acid had been produced per mole of furanoside.

Ethylene glycol (0·2 ml.) was added to part (10 ml.) of the fully oxidised solution. After 10 min., 4·5N-sulphuric acid (5 ml.) was added and the solution heated at 100° for 1·5 hr. Free iodine was extracted with chloroform, and the aqueous solution neutralised with barium carbonate. On concentration and paper chromatography and ionophoresis the filtrate was found to contain a component chromatographically identical with 3-*O*-methyl-D-glucose.

*Characterisation of the Tri- and Tetra-saccharides.*—(i) The *trisaccharide* (Found: OMe, 5·8. $C_{18}H_{31}O_{15}OMe$ requires OMe, 6·0%) showed infrared absorption peaks at 901, 843, and 761 cm.$^{-1}$ in the range 700—950 cm.$^{-1}$. The *tetrasaccharide* (Found: OMe, 4·8. $C_{24}H_{41}O_{20}$·OMe requires OMe, 4·6%) showed infrared absorption peaks at 940, 919, 844, and 765 cm.$^{-1}$ in the same range. Both the trisaccharide $\{[\alpha]_D^{20}$ +130° equil. (*c* 1·00 in $H_2O)\}$ and the tetrasaccharide fraction $\{[\alpha]_D^{20}$ +139° equil. (*c* 1·00 in $H_2O)\}$ gave less than 0·5% of ash.

(ii) *Paper chromatography and ionophoresis.* On paper chromatography in the solvent used above both the tri- and the tetra-saccharide moved as single components with $R_{Glucose}$ 0·18 and 0·054, respectively. When separated as their benzylamine derivatives [14] in the same solvent they had $R_{Glu}$ 0·35 and 0·15 respectively. The mobilities of the borate complexes [10] of the tri- and the [illegible] were 0·49 and 0·42 while those of their *N*-benzylglycosylammonium ions were 0·58 a[illegible]·47 respectively.

(iii) *Oxidation with hypoiodite.* On oxidation with alkaline hypoiodite,[6] the trisaccharide (3·6 mg.) consumed iodine equivalent to 1·30 mg. of glucose (104% of the theoretical value) while the tetrasaccharide (3·2 mg.) consumed iodine equivalent to 0·85 mg. of glucose (100%).

(iv) *Hydrolysis.* After hydrolysis as above with 1·5N-sulphuric acid at 100° for 4 hr., paper chromatography and ionophoresis showed that both the tri- and the tetra-saccharide gave only glucose and 3-*O*-methylglucose.

Portions (5 mg.) of tri- and tetra-saccharide were partially hydrolysed with N-sulphuric acid (3 ml.) at 90° for 1 hr. Paper chromatography and ionophoresis indicated that the partial

[14] Bayly and Bourne, *Nature*, 1953, **171**, 385.

XUM

hydrolysate of the trisaccharide contained glucose, 3-*O*-methylglucose, isomaltose, the disaccharide, and the original trisaccharide. The partial hydrolysate of the tetrasaccharide contained glucose, 3-*O*-methylglucose, isomaltose, the disaccharide, isomaltotriose, the trisaccharide and the original tetrasaccharide.

The trisaccharide and the tetrasaccharide were resistant when incubated with almond emulsin (as above).

(v) *Periodate oxidation.* The trisaccharide (15·7 mg.) was oxidised with 0·075M-sodium periodate (10 ml.) at 18°. The periodate consumption, expressed in moles per mole of trisaccharide, was 2·3 (0·5 hr.), 4·2 (1·0 hr.), 4·7 (3·0 hr.) and 4·8 (20 hr.). After 20 hr., 1·8 moles of formic acid had been produced per mole of trisaccharide.

One of us (P. M. G.) thanks the Department of Scientific and Industrial Research for the award of a scholarship.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM 15.
CHEMISTRY DEPARTMENT, ROYAL HOLLOWAY COLLEGE,
ENGLEFIELD GREEN, SURREY. [*Received, September 27th*, 1957.]

---

## 117. *The Reaction of Methyldisiloxanes and* 1 : 1-*Dimethyldisilthiane with Boron and Hydrogen Halides.*

By H. J. EMELÉUS and M. ONYSZCHUK.

Boron trifluoride and trichloride do not give stable addition compounds with 1 : 1′-dimethyl-, 1 : 1′ : 2 : 2′-tetramethyl-, or hexamethyl-disiloxane. Cleavage of the Si–O–Si bond occurs, with formation of the methylhalgenosilane and the methylsiloxyboron dihalide. The latter decomposes spontaneously to the methylhalogenosilane, boron trihalide, and boron trioxide. Hydrogen iodide causes cleavage of the Si–O–Si bond, but trimethylboron and methyl iodide do not react. Boron trifluoride or trichloride decomposes 1 : 1′-dimethyldisilthiane at 100°, whereas trimethylboron and methyl iodide do not react with it and hydrogen iodide cleaves the Si–S–Si bond. The absence of electron-donor activity for oxygen and sulphur in Si–O–Si and Si–S–Si linkages is discussed.

OXYGEN and sulphur atoms in dialkyl ethers and sulphides readily react with acceptor molecules, such as boron trifluoride, boron trichloride, hydrogen iodide, and alkyl halides, to form co-ordination complexes and oxonium or sulphonium compounds. This electron-donor activity of oxygen or sulphur is, however, absent in the disilyl analogues,[1] and this has been attributed in part to the ability of silicon to use its vacant 3*d*-orbitals in the formation of $\pi$-type bonds with the elements of Groups V, VI, and VII.[2] One method of increasing the electron-donor power of oxygen or sulphur when bonded to silicon might be to replace symmetrically the hydrogen atoms attached to silicon in disiloxane, $(SiH_3)_2O$, and disilthiane, $(SiH_3)_2S$, by electron-releasing methyl groups. The experiments described below were made to examine this possibility with three symmetrically substituted disiloxanes and with 1 : 1′-dimethyldisilthiane by determining if addition compounds are formed with boron trifluoride, boron trichloride, trimethylboron, hydrogen iodide, and methyl iodide.

The results showed that, unlike the diethyl ether analogue, 1 : 1′-dimethyldisiloxane did not form a stable 1 : 1 addition compound with boron trifluoride. Instead, cleavage of the Si–O–Si bond occurred at −78°. The reaction took place in two stages, but the

[1] Emeléus, MacDiarmid, and Maddock, *J. Inorg. Nuclear Chem.*, 1955, **1**, 194.
[2] Craig, Maccoll, Nyholm, Orgel, and Sutton, *J.*, 1954, 332; Stone and Seyferth, *J. Inorg. Nuclear Chem.*, 1955, **1**, 112; Aylett, Emeléus, and Maddock, *J. Inorg. Nuclear Chem.*, 1955, **1**, 187.

methylsiloxyboron difluoride formed in the first was so unstable that it could not be isolated:

$$(Me{\cdot}SiH_2)_2O + BF_3 = Me{\cdot}SiH_2{\cdot}O{\cdot}BF_2 + Me{\cdot}SiH_2F$$

$$3Me{\cdot}SiH_2{\cdot}O{\cdot}BF_2 = 3Me{\cdot}SiH_2F + BF_3 + B_2O_3$$

The possibility of the formation of a 1 : 1 adduct at low temperatures could not be eliminated, but decomposition at −78° was rapid and there was no appreciable dissociation into the original reactants. The reactions of 1 : 1′ : 2 : 2′-tetramethyldisiloxane and of hexamethyldisiloxane at −78° were very similar to that of 1 : 1′-dimethyldisiloxane. When, however, a mixture of hexamethyldisiloxane and excess of boron trifluoride was held at −78° for only 2 hr. and then cooled to −96°, excess of boron trifluoride could be pumped away, leaving a solid 1 : 1 adduct which was involatile at this temperature. When the temperature was raised to −78° most of the combined boron trifluoride was recovered unchanged, though a little reacted to form trimethylfluorosilane.

Boron trichloride with 1 : 1′-di- or 1 : 1′ : 2 : 2′-tetra-methyldisiloxane also failed to form stable 1 : 1 adducts. In the first case the main reaction at −78° was: $3(Me{\cdot}SiH_2)_2O + 2BCl_3 = 6Me{\cdot}SiH_2Cl + B_2O_3$, but it was also possible to isolate the intermediate methylsiloxyboron dichloride, though this decomposed readily at room temperature. It was, however, more stable than the difluoride. The reaction of 1 : 1′ : 2 : 2′-tetramethyldisiloxane with boron trichloride was similar, though dimethylsiloxyboron dichloride was not isolated. Wiberg and Kruerke [3] showed that an equimolecular mixture of boron tribromide and hexamethyldisiloxane formed an addition compound at −40°, which decomposed slowly to dimethylbromosilane, boron tribromide, and boron trioxide.

Neither boron trifluoride nor boron trichloride formed an addition compound at low temperatures with 1 : 1′-dimethyldisilthiane, but reaction occurred at 100° with the formation of unidentified complex organosilicon compounds. Thus the sulphur atom, in this case, shows no donor activity, though dimethyl sulphide forms a weak adduct, $Me_2S,BF_3$, which is over 90% dissociated at ordinary temperatures.[4] Methyl-substituted disiloxanes and 1 : 1′-dimethyldisilthiane did not react with trimethylboron at −78°, room temperature or 100—150°: recovery of the reactants was almost quantitative.[5] Dimethyl sulphide forms the compound $Me_2S,BMe_3$. The reaction of 1 : 1′-dimethyldisiloxane with hydrogen iodide gave a complex mixture of products, which included methyliodosilane, but with 1 : 1′-dimethyldisilthiane there was an almost quantitative formation of hydrogen sulphide and methyliodosilane: $(Me{\cdot}SiH_2)_2S + 2HI = 2Me{\cdot}SiH_2I + H_2S$. No reaction occurred with methyl iodide.

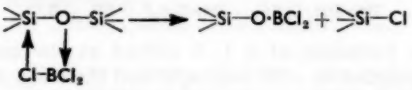
The failure of the methyl-substituted disiloxanes and disilthiane to form stable co-ordination complexes supports the current theoretical view that silicon uses its vacant 3*d*-orbitals to form bonds with oxygen and sulphur which have considerable double-bond character. Moreover, it is clear that methyl-substitution of the silicon atom does not appreciably influence the donor properties of the oxygen and sulphur atoms. For boron trifluoride, boron trichloride, and hydrogen iodide the possible formation of adducts of low stability is masked by halogenation in which silicon–oxygen bonds are broken. This occurs more readily than does the cleavage of carbon–oxygen bonds in ethers and is favoured by the larger size of the silicon atom, which favours polar attack, and also by the fact that the silicon–oxygen bond is more polar than the carbon–oxygen bond.

The mechanism which has been proposed for the reaction of alkyl ethers with boron trichloride involves an electrophilic attack by boron trichloride, with transitory formation of a carbonium cation.[6] Organosilicon compounds do not form siliconium ions,[7] and a similar mechanism is therefore unlikely in the reactions of disiloxanes with boron halides.

[3] Wiberg and Kruerke, *Z. Naturforsch.*, 1953, **8b**, 608.
[4] Graham and Stone, *Chem. and Ind.*, 1956, 319.
[5] For details of these experiments see Onyszchuk, Ph.D. Thesis, Cambridge, 1956.
[6] Gerrard and Lappert, *J.*, 1951, 1020; 1952, 1486; Gerrard, Lappert, and Silver, *J.*, 1956, 4987.
[7] Swain, Esteve, and Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 965; Eaborn, *J.*, 1953, 494.

XUM

A stepwise dehalogenation by a four-centre broadside attack, as suggested for the reaction of alcohols with boron trichloride,[8] would yield the following scheme for the interaction of boron trichloride with disiloxanes:




Since methylsiloxyboron dichlorides and the corresponding methylchlorosilanes are the first products, only the first stage of this scheme need be invoked. There is no evidence about the mechanism of decomposition of the methylsiloxyboron dichlorides. Methoxy- and ethoxy-boron dichloride yield boron oxychloride in their decomposition, and this decomposes at 70° to boron trichloride and boron trioxide.[9] No boron oxychloride was, however, isolated in the experiments described below.

Stepwise defluorination of boron trifluoride by methyldisiloxanes, yielding in the first stage a methylsiloxyboron difluoride, will also account for the reactions involving boron trifluoride. The methylsiloxyboron difluoride is less stable than the chloro-compound but the exact mechanism of its decomposition is again uncertain since no evidence was obtained in these reactions for the formation or the presence of the volatile cyclic trimeric boron oxyfluoride.[10]

## Experimental

1 : 1′-Dimethyl-disiloxane and -disilthiane were prepared by reaction of methyliodosilane with water and mercuric sulphide[11] (Found: *M*, 106·3; v. p. 190·5 mm. at 0°. Calc. for $C_2H_{10}Si_2O$: *M*, 106·2; v. p. 189·1 mm. at 0°) (Found: *M*, 122·7; v. p. 9·0 mm. at 0°. Calc. for $C_2H_{10}Si_2S$: *M*, 122·3; v. p. 8·5 mm. at 0°). 1 : 1′ : 2 : 2′-Tetramethyldisiloxane was made by hydrolysis of dimethyliodosilane[12] (Found: *M*, 134·5; v. p. 44·5 mm. at 0°. Calc. for $C_4H_{14}Si_2O$: *M*, 134·0; v. p. 44·0 mm. at 0°). Hexamethyldisiloxane was prepared by the hydrolysis of trimethylchlorosilane[13] (Found: *M*, 161. Calc. for $C_6H_{18}Si_2O$: *M*, 162). Trimethylboron was prepared by a Grignard reaction between methyl iodide and boron trichloride[14] (84% yield) (Found: *M*, 56·7; v. p. 31·3 mm. at −78°. Calc. for $C_3H_9B$: *M*, 55·9; v. p. 32·5 mm. at −78°). Hydrogen iodide was made from phosphorus iodide and water. Commercial boron trifluoride and trichloride and methyl iodide were purified by fractional condensation and distillation and checked tensimetrically before use.

*Reaction of* 1 : 1′-*Dimethyldisiloxane with Boron Trifluoride.*—Boron trifluoride (0·0829 g.) and 1 : 1′-dimethyldisiloxane (0·151 g.), held for 12 hr. at −78°, gave on distillation at −132° *methylfluorosilane* (0·157 g.) (Found: *Si*-H, by alkaline hydrolysis, 3·15; F, 29·5%; *M*, 64·7. $CH_5FSi$ requires *Si*-H, 3·14; F, 29·6%; *M*, 64·1), and a white solid which contained 81·4% of boron trioxide. Methylfluorosilane had vapour pressures (−99° to −56°) given by the equation $\log_{10} p$ (mm.) = 7·830 − 1133/*T*. The extrapolated b. p. was −44·0° ± 0·5°, the latent heat of vaporization 5190 cal./mole, and Trouton's constant 22·6. The vapour pressure at −78° was 103 mm. The m. p. was −125·0° ± 0·5°. A sample was unchanged after storage in a glass bulb at 20° in daylight for 8 weeks.

With a different ratio of reactants, boron trifluoride (0·167 g.) and 1 : 1′-dimethylsiloxane (0·400 g.) were kept at −78° overnight and methylfluorosilane (0·274 g.) (Found: *M*, 64·8. Calc. for $CH_5FSi$: *M*, 64·1) was recovered by distillation at −96°. The amount recovered was 12% in excess of that for the equation $(Me{\cdot}SiH_2)_2O + BF_3 = Me{\cdot}SiH_2F + Me{\cdot}SiH_2{\cdot}O{\cdot}BF_2$. The decomposition of methylsiloxyboron difluoride ($3Me{\cdot}SiH_2{\cdot}O{\cdot}BF_2 = 3Me{\cdot}SiH_2F + BF_3 + B_2O_3$) was confirmed by the fact that on completion of the distillation at room temperature the total recovery of methylfluorosilane (0·449 g.), which was probably contaminated with boron trifluoride, was 93%, and the yield of boron trioxide was 93% of that for the reaction

[8] Gerrard and Lappert, *J.*, 1951, 2545.
[9] Wiberg and Sutterlin, *Z. anorg. Chem.*, 1931, **202**, 1.
[10] Baumgarten and Bruns, *Ber.*, 1939, **72**, 1753.
[11] Emeléus, Onyszchuk, and Kuchen, *Z. anorg. Chem.*, 1956, **283**, 74.
[12] Emeléus and Smythe, following paper.
[13] Sauer, *J. Amer. Chem. Soc.*, 1944, **66**, 1707.
[14] Brown, *ibid.*, 1945, **67**, 374.

XUM

$3(Me{\cdot}SiH_2)_2O + 2BF_3 = 6Me{\cdot}SiH_2F + B_2O_3$. In a further experiment with 1 : 1′-dimethyldisiloxane (0·429 g.) and boron trifluoride (0·182 g.), kept for 12 hr. at −78°, methylfluorosilane (0·394 g.) (Found: *M*, 64·8) was obtained by distillation at −98° for 1 hr. Further distillation at 20° gave 0·116 g. of a product with *M*, 72·5, which gave a white deposit of boron trioxide in the molecular-weight bulb. This probably contained some of the unstable methylsiloxyboron difluoride. Measurements of the vapour pressure of an equimolar mixture of boron trifluoride and 1 : 1′-dimethyldisiloxane at −132° to −63° showed an initial v. p. of *ca.* 30 mm. at −132°, which decreased almost to zero in 2 min. The v. p. of boron trifluoride is 32 mm. at −132° and this therefore reacts rapidly with the siloxane at −132°. The vapour pressure curve of the mixture at higher temperatures was identical with that for methylfluorosilane.

*Reaction of* 1 : 1′-*Dimethyldisiloxane with Boron Trichloride.*—Boron trichloride (0·277 g.) and 1 : 1′-dimethyldisiloxane (0·206 g.) were kept at −78° for 12 hr. Distillation of the product at −78° gave methylchlorosilane (0·142 g.) (Found: *M*, 81·0. Calc. for $CH_5ClSi$: *M*, 80·4), a 91% recovery for the reaction $3(Me{\cdot}SiH_2)_2O + 2BCl_3 = 6Me{\cdot}SiH_2Cl + B_2O_3$. Further distillation at 20° gave a small fraction of *M* 130—150, which decomposed in the molecular-weight bulb and was probably the dichloro-compound, $Me{\cdot}SiH_2{\cdot}O{\cdot}BCl_2$ (*M*, 143). Boron trioxide (0·0375 g.) was also recovered. A 5 : 1 molar mixture of boron trichloride (1·675 g.) and 1 : 1′-dimethyldisiloxane (0·208 g.), after reaction at −78° for 12 hr., gave, on fractional condensation of the mixed products, a fraction condensing at −78°, which was impure methylsiloxyboron dichloride (Found: *Si*-H, 1·19; Cl, 46·7%; *M*, 146. Calc. for $CH_3OCl_2BSi$: *Si*-H, 1·41; Cl, 49·6%; *M*, 142·6). The v. p. at 0° gradually increased owing to decomposition. The material not condensed at −78° was a mixture of methylchlorosilane with excess of boron trichloride which could not be separated.

*Reaction of* 1 : 1′-*Dimethyldisiloxane with Hydrogen Iodide.*—Hydrogen iodide (0·040 g.) and 1 : 1′-dimethyldisiloxane (0·170 g.) at −78° (12 hr.) gave no hydrogen. No hydrogen iodide was recovered by distillation at −132°. Fractional distillation at higher temperatures gave inseparable mixtures, probably containing the reactants, methyliodosilane, and water [$(Me{\cdot}SiH_2)_2O + 2HI \rightleftharpoons 2Me{\cdot}SiH_2I + H_2O$)].

*Reaction of* 1 : 1′ : 2 : 2′-*Tetramethyldisiloxane with Boron Trifluoride.*—Boron trifluoride (0·343 g.) and tetramethyldisiloxane (0·226 g.) were kept at −78° for 12 hr. The white solid product when distilled at −96° gave a volatile fraction (0·399 g.) which was further separated into boron trifluoride (0·204 g.) (Found: *M*, 67·2. Calc. for $BF_3$: *M*, 67·8) and *dimethylfluorosilane* (0·170 g.) (Found: *Si*-H 1·29%; *M*, 78·6. $C_2H_7SiF$ requires *Si*-H, 1·28%; *M*, 78·1). The v. p. (−30° to −12°) was given by the equation $\log_{10} p$ (mm.) = 7·500 − 1219/*T*. The extrapolated b. p. was −9·0° ± 0·5°, the latent heat of vaporization was 5580 cal./mole, and Trouton's constant 21·1. The m. p. was −115° ± 0·5°.

The yield in the above reaction was 64% of that for the equation $3(Me_2SiH)_2O + 2BF_3 = 6Me_2SiHF + B_2O_3$, and 28% greater than that for the reaction $(Me_2SiH)_2O + BF_3 = Me_2SiH{\cdot}O{\cdot}BF_2 + Me_2SiHF$. The white solid residue from the distillation at −96° gave further volatile material at room temperature consisting of dimethylfluorosilane (0·0478 g.), boron trifluoride (0·0594 g.), and a very small fraction of *M* 124, which was probably dimethylsiloxyboron difluoride. The final white solid residue contained 97·4% of boron trioxide.

*Reaction of* 1 : 1′ : 2 : 2′-*Tetramethyldisiloxane with Boron Trichloride.*—Boron trichloride (0·148 g.) and tetramethyldisiloxane (0·170 g.) formed a colourless solution after 20 hr. at −78°. The volatile products on fractionation gave hydrogen chloride (0·0045 g.) (Found: *M*, 41·3; v. p. 19·0 mm. at −132°. Calc. for HCl: *M*, 36·5; v. p. 14·0 mm. at −132°), dimethylchlorosilane (0·0563 g.) (Found: *M*, 95·0. Calc. for $C_2H_7SiCl$: *M*, 94·6), and a fraction (0·0146 g.) with *M* 126. The last fraction, when redistilled at −23°, gave a product with *M* 163 and v. p. 7·4 mm. at 0°, which was probably dimethylsiloxyboron dichloride (*M*, 156·8) contaminated with bis(dimethoxyboron) chloride (*M*, 196). When 0·356 g. of tetramethyldisiloxane reacted at room temperature with 0·207 g. of boron trichloride the yield of dimethylchlorosilane was 63% based on the boron trichloride used in the reaction $(Me_2SiH)_2O + BCl_3 = Me_2SiHCl + Me_2SiH{\cdot}O{\cdot}BCl_2$. Fractions which probably contained dimethylsiloxyboron dichloride and bis(dimethoxyboron) chloride were again obtained but could not be further separated. The following new physical properties of dimethylchlorosilane were measured: the v. p. (−17° to 10°) was given by $\log_{10} p$ (mm). = 7·322 − 1370/*T*, the extrapolated b. p. being 34·7° ± 0·5°. The latent heat of vaporization was 6270 cal./mole, Trouton's constant 20·4 and the m. p. −111° ± 1°.

XUM

*Reaction of Hexamethyldisiloxane with Boron Trifluoride.*—Boron trifluoride (0·298 g.) and hexamethyldisiloxane (0·237 g.) were mixed at −78° and kept for 12 hr. Unchanged boron trifluoride (0·184 g.) (Found: *M*, 68·5. Calc. for $BF_3$: *M*, 67·8) was recovered by distillation at −96°. Trimethylfluorosilane (0·146 g.) (Found: *M*, 90·0. Calc. for $C_3H_9SiF$: *M*, 92·1) was isolated by distillation at −78°. These amounts are respectively 12 and 11% in excess of those calculated for the equation $(Me_3Si)_2O + BF_3 = Me_3Si{\cdot}O{\cdot}BF_2 + Me_3SiF$. A white solid residue from these distillations, when distilled at room temperature, gave trimethylfluorosilane (0·105 g.) (Found: v. p. 134 mm. at −21·5°. Calc. for $C_3H_9SiF$: v. p. 138 mm. at −21·5°). This was 77% of the amount for the decomposition $3Me_3Si{\cdot}O{\cdot}BF_2 = 3Me_3SiF + BF_3 + B_2O_3$. A second fraction (0·0146 g.; *M*, 113) probably contained trimethylsiloxyboron difluoride (Calc.: *M*, 138), but this was not isolated because of its ready decomposition. The residue was boron trioxide. The total yield of trifluoromethylsilane isolated was 96% based on the hexamethyldisiloxane used in the reaction $3(Me_3Si)_2O + 2BF_3 = 6Me_3SiF + B_2O_3$. When hexamethyldisiloxane (0·296 g.) and boron trifluoride reacted at room temperature (12 hr.) the products were trimethylfluorosilane (0·321 g.) (Found: *M*, 92·5. Calc. for $C_3H_9SiF$: *M*, 92·1) and an involatile residue (0·0425 g.) which contained 95·8% of boron trioxide. These yields were 95·6 and 97·4% respectively for the reaction: $3(Me_3Si)_2O + 2BF_3 = 6Me_3SiF + B_2O_3$. To obtain information about the initial stages of this reaction a 3 : 1 molar excess of boron trifluoride (0·399 g.) was taken with hexamethyldisiloxane (0·318 g.) and held at −78° for only 2 hr. Excess of boron trifluoride (0·277 g.) was distilled out at −96°. 0·92 Mole of boron trifluoride was consumed per mole of hexamethyldisiloxane. The temperature of the white residue was then raised to −78° and a further 0·105 g. of boron trifluoride (Found: *M*, 68·0. Calc. for $BF_3$: *M*, 67·8) was recovered with 0·0236 g. of trimethylfluorosilane (Found: *M*, 92·8. Calc. for $C_3H_9SiF$: *M*, 92·1). The boron trifluoride recovered was 97% of that taken, showing that a relatively stable 1 : 1 adduct was formed at −78°, which was readily dissociated at this temperature but not at −96°. The fluorosilane arose from the decomposition.

*Reaction of Hexamethyldisiloxane with Boron Trichloride.*—Hexamethyldisiloxane (0·455 g.) and boron trichloride (0·987 g.) gave a clear solution when left overnight at room temperature. Unchanged boron trichloride (0·668 g.) (Found: *M*, 117. Calc. for $BCl_3$: *M*, 117) was distilled off at −78°. The molar ratio for the reaction was thus almost 1 : 1. Repeated fractionation of the product gave trimethylchlorosilane (0·372 g.) (Found: *M*, 115; v. p. 63·5 mm. at 0°. Calc. for $C_3H_9SiCl$: *M*, 108·6; v. p. 74 mm. at 0°) and *trimethylsiloxyboron dichloride* (0·371 g.) (Found: Cl, 41·8%; *M*, 171; v. p. 10·5 mm. at 0°. $C_3H_9OCl_2BSi$ requires Cl, 41·4%; *M*, 170·8). The yield was 77% of that calculated for the equation $(Me_3Si)_2O + BCl_3 = Me_3Si{\cdot}O{\cdot}BCl_2 + Me_3SiCl$. The compound decomposed slowly at room temperature.

*Reaction of* 1 : 1′-*Dimethyldisilthiane with Boron Trifluoride.*—There was no reaction between 1 : 1′-dimethyldisilthiane (0·327 g.) and boron trifluoride (0·182 g.) at −78° or 20°, and the unchanged reactants were recovered quantitatively by distillation at −96°. Heating the mixture on a steam-bath for 2 hr. gave hydrogen (17·8 ml. at S.T.P.), a viscous liquid, and white crystals. The liquid product, which had the odour of a sulphide, was not fully separated and characterized. A fraction (0·298 g.) had *M*, 57·9 and a second fraction (0·0055 g.) had *M*, 151. The first would contain any residual boron trifluoride, also methylsilane and methylfluorosilane. The white crystals melted above 350°, with some decomposition. Positive tests were obtained for silicon, hydrogen bonded to silicon, and sulphur. Boron was absent. The quantities of solid and liquid were too small for a detailed examination.

*Reaction of* 1 : 1′-*Dimethyldisilthiane with Boron Trichloride.*—Boron trichloride (0·194 g.) and 1 : 1′-dimethyldisilthiane (0·202 g.) formed a white solid and a clear liquid when warmed to room temperature. The mixture was kept at 100° for 16 hr. for complete reaction. The products identified were hydrogen (18·2 ml. at S.T.P.), hydrogen chloride (0·0033 g.), and boron trichloride (0·136 g.) (Found: *M*, 117; v. p. 133·5 mm. at −23°. Calc. for $BCl_3$: *M*, 117·2; v. p. 167 mm. at −23°). A small fraction of *M* 106 may have been a mixture of boron trichloride and methylchlorosilane. The solid and viscous liquid products, which had the odour of a sulphide, were too small in amount for further separation.

*Reaction of* 1 : 1′-*Dimethyldisilthiane with Hydrogen Iodide.*—The volatile products from the reaction of 1 : 1′-dimethyldisilthiane (0·294 g.) and hydrogen iodide (0·509 g.) at room temperature during 16 hr. were hydrogen sulphide (0·0728 g.) (Found: *M*, 34·8. Calc. for $H_2S$: *M*, 34·0) and methyliodosilane (0·719 g.) (Found: *M*, 170. Calc. for $CH_5SiI$: *M*, 172). Droplets of a viscous liquid remained in the reaction vessel.

XUM

*Reaction of* 1 : 1′-*Dimethyldisilthiane with Methyl Iodide.*—Methyl iodide (0·309 g.) and 1 : 1′-dimethyldisilthiane (0·134 g.) at 100° during 16 hr. gave a small amount of transparent polymer. Methyl iodide was recovered quantitatively (Found: v. p. 141 mm. at 0°. Calc. for $CH_3I$: v. p. 141 mm. at 0°). The remaining volatile material was unchanged 1 : 1′-dimethyldisilthiane (0·105 g., 78%). There was no evidence for the formation of a sulphonium complex.

One of the authors (M. O.) is indebted to the Royal Commission for the Exhibition of 1851 for the award of an Overseas Scholarship.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 26th,* 1957.]

---

## 118. *Preparation and Properties of Dimethyliodosilane, 1 : 1′ : 2 : 2′-Tetramethyl-disiloxane and -disilthiane.*

By H. J. EMELÉUS and L. E. SMYTHE.

Dimethyliodosilane $Me_2SiHI$, 1 : 1′ : 2 : 2′-tetramethyldisiloxane $(Me_2SiH)_2O$, and 1 : 1′ : 2 : 2′-tetramethyldisilthiane $(Me_2SiH)_2S$ have been prepared and characterised. Preliminary experiments on the reaction of the disilthiane with typical acceptor compounds [Cu(I)Cl, $TiCl_4$, $PdCl_2$, and $CH_3I$] failed to show donor activity in the sulphur atom, though in some cases there were secondary reactions.

THE donor properties of the sulphur and selenium atoms in disilthiane $(SiH_3)_2S$, and its selenium analogue have already been studied [1] and it was found that iodine did not give a sulphonium or selenonium compound, as it does with the methyl analogues. Both compounds were decomposed, silyl iodide $SiH_3I$ being formed. Hydrogen iodide also caused decomposition and gave silyl iodide and hydrogen sulphide or selenide. Disilthiane did not react with silyl or methyl iodide, and with mercuric chloride it gave silyl chloride. These results showed that the silyl group had more powerful electron-attracting properties than had the methyl group. This investigation has now been extended to examine the effect of alkyl-substitution in the silyl group on the donor properties of oxygen and sulphur. Reactions with boron halides are reported separately [2] and attention is here concentrated on the reaction of 1 : 1′ : 2 : 2′-tetramethyldisilthiane with typical acceptors. The physical properties of the thiane have also been recorded, as have those of its hydrolysis product, 1 : 1′ : 2 : 2′-tetramethyldisiloxane.

Dimethylsilane was prepared by reduction of dimethyldichlorosilane or diethoxydimethylsilane with lithium aluminium hydride in ether.[3] It reacted with hydrogen iodide in the presence of aluminium iodide to give dimethyliodosilane, which was converted into 1 : 1′ : 2 : 2′-tetramethyldisiloxane by silver carbonate. The disilthiane was prepared by reaction of the iodo-compound with either black or red mercuric sulphide. Hydrolysis of 1 : 1′ : 2 : 2′-tetramethyldisilthiane to the siloxane occurred very readily and, since these two substances were difficult to separate, it was important to use dry mercuric sulphide. Disilthiane $(SiH_3)_2S$ is also readily hydrolysed.[1]

The preliminary study of the donor properties of the sulphur atom in 1 : 1′ : 2 : 2′-tetramethyldisilthiane was based on analogy with the sulphides, which form adducts with the halides of a small group of metals with relatively stable metallic sulphides. Among these are nickel, copper, silver, gold, titanium, and tin, the usual method of preparation being to add the sulphide to the metal halide in water or some other solvent. The addition compounds for which analogues were sought were $2CuCl,Me_2S$, $PdCl_2,2Me_2S$, $TiCl_4,Et_2S$, and $TiCl_4,2Et_2S$.[4] In addition, the reaction of the disilthiane with methyl iodide was

[1] Emeléus, MacDiarmid, and Maddock, *J. Inorg. Nuclear Chem.*, 1955, **1**, 194.
[2] Emeléus and Onyszchuk, preceding paper.
[3] Eaborn, *J.*, 1950, 3077.
[4] Sidgwick, "Chemical Elements and their Compounds," Oxford Univ. Press, Vol. II, p. 884; Morgan and Ledbury, *J.*, 1922, **121**, 2882.

XUM

studied. The sulphur compound was added to the anhydrous metal halide, whereas many of the adducts between alkyl sulphides and metal salts were made in aqueous solution.

With cuprous chloride the recovery of pure 1 : 1′ : 2 : 2′-tetramethyldisilthiane varied from 81 to 95%. Palladous chloride reacted more extensively, giving hydrogen, hydrogen sulphide, and a mixture of dimethylchlorosilanes and unchanged disilthiane. With titanium tetrachloride the chief product was dimethyldichlorosilane. With methyl iodide there was no reaction. These results, though they relate to a limited range of compounds and conditions, afford no evidence of donor properties in the sulphur atom. It appears that the electron-attracting power of the alkyl-substituted group is still strong enough to prevent bond formation.

## Experimental

Dimethylsilane was prepared by reducing dimethyldichlorosilane or dimethyldiethoxysilane with excess of lithium aluminium hydride in ether,[3] in ~85% yield (Found: *M*, 60·5. Calc. for $C_2H_8Si$: *M*, 60·1). The product was iodinated in the apparatus previously described,[3] a 2 : 1 mixture of dimethylsilane and hydrogen iodide being heated with freshly sublimed aluminium iodide for 12 hr. at 110°. *Dimethyliodosilane* was isolated by fractional condensation in a vacuum at −95° (Found: *Si*-H, 0·52; I, 68·4%; *M*, 186. $C_2H_7ISi$ requires *Si*-H, 0·54; I, 68·2%; *M*, 186). Hydrogen was determined by hydrolysis with 10% aqueous alkali and measurement of the hydrogen evolved. Iodine was determined volumetrically in the hydrolysate. Carbon and hydrogen were not determined by microcombustion because of explosions. The v. p. was given in the range 0—50° by: $\log_{10} p$ (mm.) = 6·928 −1479/*T*. The extrapolated b. p. was 92° ± 1°, the latent heat of vaporisation 6760 cal./mole, Trouton's constant 18·5, the v. p. at 0° was 32 ± 0·5 mm., and the m. p. −88° ± 0·5°. In the fractionation a second product, which separated during the fractional condensation in a trap cooled at −22°, was probably dimethyldi-iodosilane but was not fully characterised.

*Preparation of* 1 : 1′ : 2 : 2′-*Tetramethyldisiloxane*.—Dimethyliodosilane (2—8 g.) was passed as vapour through a tube packed with dried silver carbonate (20 g.) and powdered glass. One passage gave a good conversion. Fractional condensation in a trap cooled to −95° gave a 70% yield of 1 : 1′ : 2 : 2′-*tetramethyldisiloxane* based on the equation $2Me_2SiHI + Ag_2CO_3 = (Me_2SiH)_2O + 2AgI + CO_2$. It was analysed by alkaline hydrolysis and measurement of the hydrogen liberated, followed by gravimetric estimation of silica in the hydrolysate (Found: *Si*-H, 1·46; Si, 41·5%; *M*, 133. $C_4H_{14}OSi_2$ requires *Si*-H, 1·46; Si, 41·5%; *M*, 134). The v. p. was given in the range 0—50° by $\log_{10} p$ (mm.) = 7·464 − 1585/*T*. The extrapolated b. p. was 73° ± 1°, the latent heat of vaporisation 7250 cal./mole, Trouton's constant 21, and the v. p. at 0° was 46 ± 0·5 mm. Samples were unchanged when stored in glass for 2—3 weeks, but later small amounts of hydrogen were liberated.

*Preparation of* 1 : 1′ : 2 : 2′-*Tetramethyldisilthiane*.—Dimethyliodosilane (2—8 g.) was passed as vapour through a tube closely packed with dry mercuric sulphide and a large excess of powdered glass. The yield did not depend on whether red or black mercuric sulphide was used. The product and unchanged reactant were condensed and then passed again through the tube. The desired product was separated by fractional condensation in traps cooled severally at −22°, −45°, and −95°. The first retained 70% of the total product, including most of the thiane. The other traps retained small amounts of unchanged iodide mixed with thiane; a small amount of hydrogen sulphide, formed by reaction of the thiane with traces of water, was condensed in liquid nitrogen. The product in the first trap, purified by fractional condensation at −22°, gave 1 : 1′ : 2 : 2′-*tetramethyldisilthiane* [65—70% based on the reaction $2Me_2SiHI + HgS = (Me_2SiH)_2S + HgI_2$ (Found: *Si*-H, 1·45; Si, 36·6; S, 20·8%; *M*, 150. $C_4H_{14}SSi_2$ requires *Si*-H, 1·33; Si, 37·4; S, 21·3%; *M*, 150)]. Sulphur was determined in the hydrolysate by oxidation with bromine water and precipitation as $BaSO_4$. The v. p. was given in the range 0—50° by $\log_{10} p$ (mm.) = 6·461 −1498/*T*. The extrapolated b. p. was 145° ± 1°, the latent heat of vaporisation 6850 cal./mole, and Trouton's constant 16·4, the v. p. at 0° was 9·0 ± 0·5 mm., and the m. p. −146° ± 0·1°.

The infrared spectra of the above new compounds will be reported elsewhere.

*Reaction of* 1 : 1′ : 2 : 2′-*Tetramethyldisilthiane with Metallic Salts*.—In three experiments

[3] Emeléus, Onyszchuk, and Kuchen, *Z. anorg. Chem.*, 1956, **283**, 74.

in which dry cuprous chloride (0·350, 0·224, 0·140 g.) was treated in a sealed tube with 1 : 1′ : 2 : 2′-tetramethyldisilthiane (0·428, 0·970, 0·613 g.) the weights of the latter recovered were 0·407, 0·920, and 0·610 g. The purity of the recovered material was checked by the v. p. at 0° and the molecular weight. In the first experiment the tube was held for 12 hr. at 40° and in the other two it was shaken at room temperature.

Titanium tetrachloride (0·120 g.) and 1 : 1′ : 2 : 2′-tetramethyldisilthiane (0·680 g.) showed no sign of reaction at −20° (1 hr.). At 0° a vigorous reaction occurred, the volatile products being unchanged 1 : 1′ : 2 : 2′-tetramethyldisilthiane (0·455 g.) (Found: *M*, 150; v. p. 9 mm. at 0°. Calc. for $C_4H_{14}SSi_2$: *M*, 150; v. p. 9 mm. at 0°) and dimethyldichlorosilane (Found: *M*, 129; v. p. 42 mm. at 0°. Calc. for $C_2H_6Cl_2Si$: *M*, 129; v. p. 40 mm. at 0°). A further fraction (0·047 g.) probably also contained dimethyldichlorosilane.

Palladous chloride (0·990 g.) and excess of 1 : 1′ : 2 : 2′-tetramethyldisilthiane reacted vigorously at room temperature, yielding a grey-black solid. The volatile products were hydrogen sulphide (0·029 g.) (Found: *M*, 34·1. Calc. for $H_2S$: *M*, 34·1) and a fraction (0·965 g.) of *M* 118 containing 39·6% of Cl, which was probably impure dimethyldichlorosilane (*M*, 128; Cl, 55%), but could not be further purified by vacuum-fractionation.

Methyl iodide (0·948 g.) was sealed with 1 : 1′ : 2 : 2′-tetramethyldisilthiane (0·581 g.) and kept at 40° (100 hr.). The liquids were miscible. Fractionation of the products gave only the tetramethyldisilthiane (0·560 g.) (Found: *M*, 149; v. p. 9 mm. at 0°) and methyl iodide (0·920 g.) (Found: *M*, 142; v. p. 134 mm. at 0°. Calc. for $CH_3I$: *M*, 142; v. p. 141 mm. at 0°).

One of the authors (L. S.) is indebted to the Chemical Society for the award of the Corday–Morgan Studentship.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 26th*, 1957.]

---

## 119. *Complex Fluorides of Quadrivalent Osmium and Iridium and the Corresponding Free Acids.*

By M. A. HEPWORTH, P. L. ROBINSON, and G. J. WESTLAND.

Complex fluorides of osmium and iridium, $M^I_2M^{IV}F_6$, where $M^I$ is $NH_4$, $Me_4N$, or Na, and aqueous solutions of the corresponding fluoro-acids $H_2OsF_6$ and $H_2IrF_6$ were prepared. The lattice constants and some other properties of several of the compounds are given.

THE method of obtaining complexes of quadrivalent osmium and iridium used [1] to prepare the hexafluoro-osmates(v) and -iridates(v) and, from them by reaction with water, the corresponding hexafluoro-osmates(IV) and -iridates(IV), readily yields the sparingly soluble salts of the higher alkali metals but fails for cations whose salts are rather soluble (*e.g.*, sodium) or of which the corresponding quinquevalent complex has not been obtained (*e.g.*, ammonium, tetramethylammonium). Salts of these cations can be conveniently prepared from the appropriate free acid.

The marked resistance of the hexafluoroplatinates(IV) to hydrolysis noted by Sharpe [2] has been used by Clarke and Perros [3] to isolate the free crystalline acid by ion exchange. A similar stability of hexafluoro-iridates(IV) and -osmates(IV) in aqueous solution allows solutions of their free acids to be prepared by ion exchange, but does not permit the isolation of the crystalline acid; all attempts to evaporate the aqueous solution resulted in decomposition. Conductivity data for hexafluoroiridic acid show that the plot of $\Lambda$ against $\sqrt{c}$ is linear below 0·0015M, and that it is an acid comparable in strength with other strong dibasic fluoro-acids of this type; this also accords with the low solubilities of its higher alkali-metal salts.

The very high equivalent conductance of the acid at infinite dilution ($\Lambda_0 = 580$

[1] Hepworth, Robinson, and Westland, *J.*, 1954, 4268.
[2] Sharpe, *J.*, 1950, 3444.
[3] Clarke and Perros, *J. Amer. Chem. Soc.*, 1953, **75**, 5734.

ohm$^{-1}$ cm.$^2$) which, if it were behaving as a dibasic acid, would represent the palpably incorrect ion conductance, $\lambda_0^-$, of 230 ohm$^{-1}$ cm.$^2$ for the $\frac{1}{2}IrF_6^{2-}$ anion, indicates progressive hydrolysis of the original anion. The potentiometric titration of the acid with sodium hydroxide gives a pH curve typical of a mixture containing both a strong and a weak acid. Thus the apparent basicity of the acid is raised, and when this approaches 3 the apparent ion conductance of the anion would be about the value observed. It is suggested that on dilution the hexafluoroiridate(IV) ion dissociates:

$$IrF_6^{2-} + H_2O \rightleftharpoons IrOHF_5^{2-} + H^+ + F^-$$

Aqueous solutions of hexafluoro-platinic, -iridic and -osmic acids are yellow, but are distinguishable by their absorption spectra. Thus the hexafluoroplatinate(IV) ion has two absorption peaks of comparable intensity (279 mμ and 318 mμ [3]); the hexafluoroiridate(IV) ion a strong peak at 213 mμ and a much weaker one at 316 mμ; and the hexafluoro-osmate(IV) ion a strong peak below 200 mμ and a very weak one at 308 mμ, so we deduced that the hexafluororhenate(IV) ion would not absorb above 200 mμ; this has been confirmed by use of cæsium hexafluororhenate, $Cs_2ReF_6$.

*Unit-cell dimensions of the* $M_2PtF_6$,[4] $M_2IrF_6$, $M_2OsF_6$, *and* $M_2ReF_6$ [5] *series* (Å).

| | $Na_2$ | $K_2$ | $(NH_4)_2$ | $Rb_2$ | $Cs_2$ | $(Me_4N)_2$ |
|---|---|---|---|---|---|---|
| $PtF_6^{2-}$ hexagonal | $a = 9{\cdot}41$, $c = 5{\cdot}16$ | $a = 5{\cdot}76$, $c = 4{\cdot}64$ | — | $a = 5{\cdot}96$, $c = 4{\cdot}83$ | $a = 6{\cdot}22$, $c = 5{\cdot}01$ | — |
| $IrF_6^{2-}$ hexagonal | $a = 9{\cdot}34$, $c = 5{\cdot}14$ | $a = 5{\cdot}80$, $c = 4{\cdot}63$ | $a = 5{\cdot}98$, $c = 4{\cdot}79$ | $a = 5{\cdot}97$, $c = 4{\cdot}79$ | $a = 6{\cdot}24$, $c = 5{\cdot}00$ | — |
| cubic | — | — | — | — | — | $a = 11{\cdot}41$ |
| $OsF_6^{2-}$ hexagonal | — | $a = 5{\cdot}80$, $c = 4{\cdot}62$ | — | — | $a = 6{\cdot}26$, $c = 5{\cdot}00$ | — |
| $ReF_6^{2-}$ hexagonal | — | $a = 5{\cdot}86$, $c = 4{\cdot}60$ | $a = 6{\cdot}06$, $c = 4{\cdot}77$ | $a = 6{\cdot}01$, $c = 4{\cdot}77$ | $a = 6{\cdot}32$, $c = 4{\cdot}99$ | — |

Crystallographically, the salts of the hexafluoro-iridate(IV) and -osmate(IV) ions closely resemble those of other hexafluoro-(IV)-acids; the unit-cell sizes for some alkali-metal and ammonium salts are shown in the Table, for comparison with those of the hexafluoroplatinate(IV) and hexafluororhenate(IV) series.

The potassium, ammonium, rubidium, and cæsium salts are all of the hexagonal $K_2GeF_6$ type,[6] but sodium hexafluoroiridate(IV) is isostructural with a series of sodium and lithium salts which includes sodium hexafluoroplatinate(IV).[7]

Cæsium hexafluoroiridate(IV) is paramagnetic with $\mu = 1{\cdot}42$ B.M., much lower than the calculated value of 1·73 B.M. required for the presence of one unpaired electron. This depression is peculiar, especially in light of the much better agreement with the theoretical value found in those hexachloroiridates(IV) which have been examined; thus in $(NH_4)_2IrCl_6$, $\mu = 1{\cdot}67$ and in $K_2IrCl_6$, $\mu = 1{\cdot}65$ B.M.[8]

## Experimental

*Preparation of the Free Acids.*—(a) *Hexafluoroiridic.* Sodium hexafluoroiridate(V), prepared as described previously,[1] was treated with distilled water and, when reaction was complete, the solution was passed at the rate of 2—3 ml./min. through a 1·5 × 40 cm. column of Zeo-Karb 225 resin in the hydrogen form. The column was eluted with water until the eluate ceased to be yellow and acid to litmus. After dilution to a known volume, the concentration of the acid

[4] Sharpe, *J.*, 1953, 197.
[5] Peacock, personal communication.
[6] Cox and Sharpe, *J.*, 1953, 1783.
[7] Cox, *J.*, 1954, 3251.
[8] Mellor, *J. Proc. Roy. Soc. New South Wales*, 1943, **77**, 150.

in the solution was determined by evaporating an aliquot portion to dryness in a platinum dish and weighing the iridium metal produced after reduction in hydrogen.

Attempts were made to isolate the crystalline acid by (1) evaporation of the solution in a vacuum over sodium hydroxide pellets, and (2) slow evaporation in a Polythene vessel at room temperature with added hydrofluoric acid; both yielded only violet-red iridium(IV) oxide.

(b) *Hexafluoro-osmic.* An aqueous solution of this acid was made similarly from potassium hexafluoro-osmate(IV), but again the acid could not be isolated.

*Potassium, Rubidium, and Cæsium Hexafluoro-osmates*(IV) *and -iridates*(IV).—These salts were prepared directly from the corresponding quinquevalent derivatives as described previously.[1] Approximate solubilities of $K_2IrF_6$ and $Cs_2IrF_6$ were obtained by measuring the concentration of their saturated aqueous solutions at room temperature (Found: $K_2IrF_6$, 1·2 g./100 ml. of solution; $Cs_2IrF_6$, 0·7 g./100 ml. of solution).

*Sodium, Ammonium, and Tetramethylammonium Hexafluoroiridates*(IV).—The calculated quantity of aqueous 0·05N-sodium hydroxide required to neutralise 20 ml. of a solution of hexafluoroiridic acid was slowly added to the latter with stirring to avoid local concentration of the alkali and thereby to minimise hydrolysis. Any suspended matter was filtered off and the filtrate evaporated to dryness in a vacuum over sodium hydroxide pellets. The residue, an almost white powder, consisted of *sodium hexafluoroiridate*(IV) (Found: Ir, 54·9; F, 32·8. $Na_2IrF_6$ requires Ir, 54·7; F, 32·3%). By proceeding exactly analogously and neutralising with the appropriate hydroxide, the corresponding *ammonium* and *tetramethylammonium salts* were obtained, the first as a pale violet powder and the second as large well-formed yellow cubes {Found: Ir, 56·0; F, 33·8. $(NH_4)_2IrF_6$ requires Ir, 56·3; F, 33·2%. Found: Ir, 42·0; F, 24·1. $[(CH_3)_4N]_2IrF_6$ requires Ir, 42·5; F, 25·0%}.

All these salts were readily soluble in water and easily hydrolysed in alkali. The ammonium salt was heated in a vacuum through a rising range of temperature; it decomposed suddenly at 220°, with visible volatilisation of ammonium fluoride, and left a black residue; *X*-ray examination revealed this to be iridium metal entirely free from any iridium trifluoride.

*Absorption Spectra and X-Ray Photographs.*—Ultraviolet absorption spectra of both series of salts were measured on a Model S.P. 500 Unicam spectrophotometer at 200—350 mμ with matched 1 cm. cells. Measurements were made on solutions of the free acids and their salts covering a range of concentrations; Beer's law was obeyed.

Specimens for *X*-ray photographs were packed in thin-walled (0·5 mm.) Pyrex glass capillaries. A 19 cm. camera, provided with iron radiation rendered monochromatic by lithium fluoride, was used.

We thank Professor R. S. Nyholm for magnetic measurements, Dr. R. D. Peacock for a specimen of $Cs_2ReF_6$, and Imperial Chemical Industries, General Chemicals Division, for the fluorine cell. The work was done during the tenure of a British Titan Products Fellowship (M. A. H.).

Department of Chemistry, King's College,
Newcastle upon Tyne.

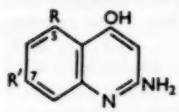
[*Received, August 27th*, 1957.]

## 120. *Cyclic Amidines. Part VI.* 5- and 7-Substituted 2-Amino-4-hydroxyquinolines.*

By R. Hardman and M. W. Partridge.

The formation of 5- and 7-substituted 2-amino-4-hydroxyquinolines by the interaction of ethyl cyanoacetate and the benzenesulphonates of *meta*-substituted arylamines has been examined. From these salts of *m*-toluidine and of *m*-chloroaniline, both isomerides were produced, whereas the salts of *m*-anisidine and of *m*-aminophenol gave only 7-substituted aminohydroxyquinolines.

In Part II [1] we described the production of 2-amino-4-hydroxyquinolines by interaction of ethyl cyanoacetate or an α-substituted ethyl cyanoacetate with an arylammonium arenesulphonate. We have now examined the reaction between *meta*-substituted arylammonium benzenesulphonates and ethyl cyanoacetate in which either a 5- or a 7-substituted quinoline can be formed. By this reaction, the benzenesulphonates of *m*-toluidine and *m*-chloroaniline furnished both isomerides (I; R = Me or Cl, R′ = H and R′ = Me or Cl, R = H), the major component of the mixture, as shown by orientation, being the 7-substituted quinoline. From *m*-aminophenol and *m*-anisidine salts, only 7-substituted quinolines (I; R′ = OH or OMe, R = H) were formed.



(I)

Degradations of 2-amino-4-hydroxyquinoline and its derivatives were studied as models for the orientation of its 5- and 7-substituted derivatives. Its hydrolysis to 2 : 4-dihydroxyquinoline was effected in only moderate yield by potash fusion. Oxidation by permanganate furnished a mixture from which 4-hydroxyquinazoline and 2 : 4-dihydroxyquinazoline were isolated. The formation of the quinazoline ring apparently involved an initial oxidative fission of the 3 : 4-bond of the quinoline, followed by a recyclisation of the resulting aminodicarboxylic acid; in agreement, oxalylanthranilic acid, previously recognised as an oxidation product of 4-hydroxyquinoline,[2] was also isolated from the oxidation products. The heterocyclic ring exhibited a resistance to reduction similar to that reported for other 4-hydroxyquinolines; [3] the product of reduction with Raney alloy and alkali [4] was evidently 2-amino-5 : 6 : 7 : 8-tetrahydro-4-hydroxyquinoline.

3-Bromo-2 : 4-dihydroxyquinoline readily afforded 2 : 4-dihydroxyquinoline on reduction with Raney alloy and alkali,[5] but with 2 : 4-dichloroquinolines the yields of reduction products were low. In the latter cases, halogen was removed by tin and hydrochloric acid.[6]

Peroxide oxidation of quinisatin oxime, produced by treatment of 2-amino-4-hydroxyquinoline with nitrous acid,[1] was unsatisfactory, since it gave only 2 : 4-dihydroxy-3-nitroquinoline. No recognisable product was obtained when degradation of this oxime *via* a Beckmann transformation was attempted.

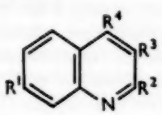
For orientation 2-amino-4-hydroxy-7-methylquinoline (I; R′ = Me, R = H) was brominated to its 3-bromo-derivative (II; $R^1$ = Me, $R^2$ = $NH_2$, $R^3$ = Br, $R^4$ = OH) which with nitrous acid furnished the bromodihydroxyquinoline (II; $R^1$ = Me, $R^2$ = $R^4$ = OH, $R^3$ = Br); removal of the bromine by reduction with Raney alloy [5] gave the dihydroxyquinoline (II; $R^1$ = Me, $R^2$ = $R^4$ = OH, $R^3$ = H), and the dichloroquinoline (II; $R^1$ = Me, $R^2$ = $R^4$ = Cl, $R^3$ = H), obtained by interaction of this

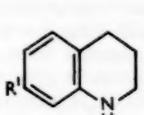
* Part V, *J.*, 1957, 2888.

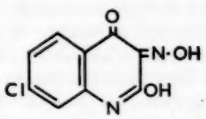
[1] Hardman and Partridge, *J.*, 1954, 3878.
[2] Kretschy, *Monatsh.*, 1883, **4**, 156; 1884, **5**, 16.
[3] Cavallito and Haskell, *J. Amer. Chem. Soc.*, 1944, **66**, 1166.
[4] Cf. Papa, Schwenk, and Breiger, *J. Org. Chem.*, 1949, **14**, 366.
[5] Cf. Schwenk, Papa, and Ginsberg, *Ind. Eng. Chem. Anal.*, 1943, **15**, 576.
[6] Gabriel and Thieme, *Ber.*, 1919, **52**, 1079.

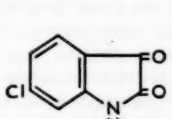
dihydroxyquinoline and phosphorus oxychloride, was reduced to 1 : 2 : 3 : 4-tetrahydro-7-methylquinoline (III; $R^1$ = Me). This was characterised by comparison of its benzoyl derivative, hydrochloride, and picrate with authentic specimens. The second methylquinoline formed from *m*-toluidine was therefore the 5-methyl derivative.

2-Amino-4-hydroxy-7-methoxyquinoline (I; R′ = MeO, R = H) with phosphorus oxychloride yielded a chloro-compound (II; $R^1$ = MeO, $R^2$ = $NH_2$, $R^3$ = H, $R^4$ = Cl), the amino-group of which was replaced by hydroxyl on treatment with nitrous acid. This chlorohydroxyquinoline (II; $R^1$ = MeO, $R^2$ = OH, $R^3$ = H, $R^4$ = Cl) was converted *via* the dichloroquinoline (II; $R^1$ = MeO, $R^2$ = $R^4$ = Cl, $R^3$ = H) into 1 : 2 : 3 : 4-tetrahydro-7-methoxyquinoline (III; $R^1$ = MeO) which afforded a benzoyl derivative, a hydrochloride, and a picrate identical with those derived from authentic 7-methoxyquinoline.


(II)


(III)


(IV)


(V)

The orientation of the hydroxyquinoline prepared from *m*-aminophenol (I; R′ = OH, R = H) followed from that of its orientated homologue (I; R′ = OMe, R = H), since the product of demethylation of the latter furnished a base, hydrochloride, and picrate identical with those derived from the former. The identical orientation of the quinolines produced from *m*-anisidine and *m*-aminophenol was confirmed by demethylation of 2-amino-4-chloro-7-methoxyquinoline (II; $R^1$ = MeO, $R^2$ = $NH_2$, $R^3$ = H, $R^4$ = Cl) to the same chlorohydroxyquinoline (II; $R^1$ = OH, $R^2$ = $NH_2$, $R^3$ = H, $R^4$ = Cl) as was formed when the aminodihydroxyquinoline (I; R′ = OH, R = H) was treated with phosphorus oxychloride. Further, hydrolysis of this chlorohydroxyquinoline (II; $R^1$ = OH, $R^2$ = $NH_2$, $R^3$ = H, $R^4$ = Cl) furnished the original dihydroxyquinoline (I; R′ = OH, R = H). The chlorohydroxyquinoline (II; $R^1$ = OH, $R^2$ = $NH_2$, $R^3$ = H, $R^4$ = Cl) could not be converted into the dichloroquinoline (II; $R^1$ = $R^4$ = Cl, $R^2$ = $NH_2$, $R^3$ = H) for comparison with the compound formed by interaction of 2-amino-7-chloro-4-hydroxyquinoline (I; R′ = Cl, R = H) and phosphorus oxychloride.

2-Amino-7-chloro-4-hydroxyquinoline (I; R′ = Cl, R = H) with nitrous acid gave 7-chloro-3 : 4-dihydro-2-hydroxy-3-hydroxyimino-4-oxoquinoline (IV), which on being boiled with sulphuric acid yielded 6-chloroisatin (V). Analogous conversions of quinoline derivatives into isatin derivatives have been previously reported.[7] This isatin derivative was smoothly oxidised by hydrogen peroxide to 4-chloroanthranilic acid and the latter by deamination gave 4-chlorobenzoic acid. The isomeric aminochlorohydroxyquinoline derived from *m*-chloroanilinium benzenesulphonate and ethyl cyanoacetate was accordingly the 5-chloro-derivative.

Most of the quinoline derivatives described in this communication were examined for amœbacidal activity; none was observed.

## Experimental

*Oxidation of 2-Amino-4-hydroxyquinoline.*—(i) 2-Amino-4-hydroxyquinoline (4 g.) in a solution of potassium hydroxide (2·8 g.) in water (270 ml.) was treated at room temperature during 4 days with N-potassium permanganate (600 ml.). The suspension was filtered, concentrated, and neutralised with sulphuric acid. Amphoteric material was extracted from the precipitate with aqueous sodium hydroxide and reprecipitated; this on recrystallisation from ethanol gave 4-hydroxyquinazoline (1·0 g., 27%), m. p. and mixed m. p. 219—220° [Found: C, 65·8; H, 4·4; N, 19·2%; *M* (ebullioscopic), 140. Calc. for $C_8H_6ON_2$: C, 65·8; H, 4·1; N,

[7] Lahey, Lamberton, and Price, *Austral. J. Sci. Res.*, 1950, *A*, **3**, 155.

19·2%; *M*, 146]; its picrate had m. p. and mixed m. p. 207—208°. The mother-liquor from the isolation of the amphoteric material, after completion of the removal of manganese dioxide, concentration, and acidification, furnished hydrated oxalylanthranilic acid (0·5 g., 10%), m. p. and mixed m. p. 195—196° (decomp.).

(ii) Water-soluble material obtained from an oxidation at 85—90° for 30 min., on being boiled for 90 min. with concentrated hydrochloric acid, gave as a water-soluble fraction 4-hydroxyquinazoline (0·5 g., 14%), m. p. and mixed m. p. 219—220°, and as a water-insoluble fraction, purified by sublimation *in vacuo*, 2 : 4-dihydroxyquinazoline (0·6 g., 15%), plates, m. p. and mixed m. p. 355° (decomp.) (from ethyl acetate) (Found: C, 59·8; H, 3·7; N, 17·0. Calc. for $C_8H_6O_2N_2$: C, 59·3; H, 3·7; N, 17·3%), $\lambda_{max.}$ (in EtOH) 217 (ε 40,000), 310 mμ (ε 3400); authentic 2 : 4-dihydroxyquinazoline had $\lambda_{max.}$ 217 (ε 42,600), 310 mμ (ε 3600); the 3-methyl derivative had m. p. and mixed m. p. 229—232°.

2-*Amino*-5 : 6 : 7 : 8-*tetrahydro*-4-*hydroxyquinoline*.—A solution of 2-amino-4-hydroxyquinoline (12 g.) in 10% aqueous sodium hydroxide (360 ml.) was treated at 85° during 7 hr. with Raney alloy (51 g.), stirred for a further 2 hr., and filtered. The precipitate obtained by neutralisation was freed from 2-amino-4-hydroxyquinoline by the addition of chloroform to a methanol solution and then gave the *tetrahydroquinoline* (6 g., 49%) as prisms, m. p. 335—336° (decomp.), from aqueous ethanol (Found: N, 16·9. $C_9H_{12}ON_2$ requires N, 17·1%). This compound was insoluble in aqueous sodium carbonate, soluble in aqueous sodium hydroxide, and gave a ferric colour similar to that of 2-amino-4-hydroxyquinoline, but on pyrolysis evolved ammonia less readily. Its *picrate*, needles from aqueous ethanol, had m. p. 252° (decomp.) (Found: C, 45·8; H, 4·1; N, 17·5. $C_{15}H_{15}O_8N_5$ requires C, 45·8; H, 3·8; N, 17·8%); the *hydrochloride* formed prisms, m. p. 244—246° (decomp.), from hydrochloric acid (Found: C, 53·7; H, 6·2. $C_9H_{13}ON_2Cl$ requires C, 53·8; H, 6·5%). With nitrous acid, it gave 3 : 4 : 5 : 6 : 7 : 8-*hexahydro*-2-*hydroxy*-3-*hydroxyimino*-4-*oxoquinoline* as purple prisms, m. p. above 400° (from dimethylformamide) (Found: C, 55·6; H, 4·7; N, 14·9. $C_9H_{10}O_3N_2$ requires C, 55·7; H, 5·2; N, 14·4%); this compound did not give a positive Liebermann's test. The *acetyl derivative*, plates, m. p. 137°, from aqueous ethanol (Found: C, 63·9; H, 6·9. $C_{11}H_{14}O_3N_2$ requires C, 64·1; H, 6·8%), was soluble in aqueous alkalis. Under Schotten–Baumann conditions, it formed an alkali-insoluble *dibenzoyl derivative* [prisms, m. p. 158—159°, from ethanol (Found: C, 74·6; H, 5·7; N, 7·8. $C_{23}H_{20}O_3N_2$ requires C, 74·2; H, 5·4; N, 7·5%)].

2-Amino-4-hydroxyquinoline was apparently unaffected on treatment with benzoyl chloride under Schotten–Baumann conditions, but on being warmed with benzoyl chloride gave a *monobenzoyl derivative hydrochloride* (50%), prisms, m. p. 191—192° (from methanol–benzene) (Found: C, 64·0; H, 4·5; N, 9·1. $C_{16}H_{13}O_2N_2Cl$ requires C, 63·9; H, 4·4; N, 9·3%); the free (N- or O-)*benzoyl derivative* formed prisms, m. p. 121—123°, from benzene–light petroleum (Found: C, 72·7; H, 4·7; N, 10·2. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·6; N, 10·6%). This compound readily formed 2-amino-4-hydroxyquinoline with aqueous alkali.

3-*Bromo*-2 : 4-*dichloroquinoline*.—3-Bromo-2 : 4-dihydroxyquinoline [8] when boiled with phosphorus oxychloride for 6 hr. furnished the 2 : 4-*dichloroquinoline* (87%), needles (from ethanol), m. p. 95°, b. p. 157—158°/1·5 mm. (Found: C, 39·4; H, 1·6; halogen, 54·5. $C_9H_4NCl_2Br$ requires C, 39·0; H, 1·5; halogen, 54·5%).

2 : 4-*Dihydroxyquinoline*.—(i) 3-Bromo-2 : 4-dihydroxyquinoline (20·6 g.) in 10% aqueous sodium hydroxide (600 ml.) was heated at 90° with Raney alloy [5] (75 g.) during 2½ hr., stirring was continued for a further 1 hr., and the mixture was filtered. On acidification, the filtrate yielded 2 : 4-dihydroxyquinoline (10·6 g., 77%) which was identified as its monoacetate, m. p. and mixed m. p. 214—215°. This reduction could not be effected with sodium and ethanol, or sodium and *iso*pentyl alcohol.

(ii) 2-Amino-4-hydroxyquinoline was fused at 250—290° with potassium hydroxide for 3 hr.; the acid-insoluble fraction recovered from the melt gave 2 : 4-dihydroxyquinoline (37%), which was characterised as its monoacetate. This hydrolysis could not be effected with potassium hydroxide in water or in ethylene glycol.

1 : 2 : 3 : 4-*Tetrahydroquinoline*.—(i) Quinoline on being reduced with Raney alloy [4,5] gave its 1 : 2 : 3 : 4-tetrahydro-derivative (87%) which was characterised as its picrate,[9] m. p. 141·5—143·5°, and its benzoyl derivative,[10] m. p. 76°.

[8] Hardman and Partridge, *J.*, 1955, 510.
[9] Ishii, *J. Pharm. Soc. Japan*, 1952, **72**, 1317.
[10] Hoffmann and Königs, *Ber.*, 1883, **16**, 727.

(ii) 2 : 4-Dichloroquinoline, reduced in the same way,[4,5] yielded quinoline (4%), 1 : 2 : 3 : 4-tetrahydroquinoline (22%), and unchanged dichloro-compound (44%). When the reduction was effected in the presence of ethanol, in addition to the tetrahydroquinoline (16%), another base, probably 4-ethoxyquinoline, was recovered as its *picrate*, m. p. 195° (Found: C, 51·0; H, 3·4; N, 13·9. $C_{17}H_{14}O_8N_4$ requires C, 50·8; H, 3·5; N, 13·9%). Reduction with tin and hydrochloric acid [6] led to 1 : 2 : 3 : 4-tetrahydroquinoline (74%) and quinoline (4%).

(iii) 3-Bromo-2 : 4-dichloroquinoline by the same method [6] of reduction gave 1 : 2 : 3 : 4-tetrahydroquinoline (52%) and quinoline (3%), whereas, with Raney alloy,[4,5] the products were 2 : 4-dichloroquinoline [11] (12%), m. p. and mixed m. p. 67°, and quinoline (2%).

*2-Amino-4-chloroquinoline.*—2-Amino-4-hydroxyquinoline (6·4 g.) was refluxed for 8 hr. with phosphorus oxychloride (40 ml.). After removal of the excess of phosphorus oxychloride *in vacuo*, the solid, phosphorus-containing residue was boiled with water for 1 hr. and basified with sodium hydroxide. The gelatinous *chloroquinoline* after being collected in chloroform crystallised from benzene–light petroleum as prisms, m. p. 136° (4·4 g., 62%) (Found: N, 15·3; Cl, 19·9. $C_9H_7N_2Cl$ requires N, 15·7; Cl, 19·9%); it gave a *hydrochloride*, needles, m. p. 207—208°, from hydrochloric acid (Found: N, 12·9. $C_9H_8N_2Cl_2$ requires N, 13·0%), *benzenesulphonate*, prisms, m. p. 168°, from aqueous propan-2-ol (Found: C, 52·5; H, 4·5; N, 7·5. $C_{15}H_{13}O_3N_2ClS,0{\cdot}5H_2O$ requires C, 52·1; H, 4·1; N, 8·1%), and *picrate*, prisms, m. p. 279—280° (decomp.), from glacial acetic acid (Found: C, 44·4; H, 2·6; N, 16·9; Cl, 8·9. $C_{15}H_{10}O_7N_5Cl$ requires C, 44·2; H, 2·5; N, 17·2; Cl, 8·7%). The chloroquinoline was stable to hydriodic acid and to aqueous alkali but gave 2-amino-4-hydroxyquinoline on being boiled with potassium hydroxide in ethylene glycol. When refluxed for 20 hr. with sodium propoxide in propan-1-ol, it furnished 2-amino-4-*n*-propoxyquinoline [8] (78%).

The following *benzenesulphonates* were prepared: m-*chloroanilinium*, plates, m. p. 203°, from propan-2-ol (Found: N, 4·8. $C_{12}H_{10}O_3NClS$ requires N, 4·9%); m-*hydroxyanilinium*, prisms, m. p. 187·5—188°, from methanol–ethyl acetate (Found: C, 54·1; H, 4·8. $C_{12}H_{11}O_4NS$ requires C, 53·9; H, 4·9%); m-*methoxyanilinium*, needles, m. p. 173·5—174·5°, from propan-2-ol (Found: C, 55·7; H, 5·3. $C_{13}H_{13}O_4NS$ requires C, 55·5; H, 5·4%); m-*methylanilinium*, plates, m. p. 170°, from propan-2-ol (Found: C, 59·0; H, 5·9. $C_{13}H_{13}O_3NS$ requires C, 58·9; H, 5·7%).

*2-Amino-4-hydroxy-5- and -7-methylquinoline.*—Ethyl cyanoacetate (22·6 g.) and *m*-methylanilinium benzenesulphonate (53 g., 1 mol.) were heated together at 210° for 1 hr. A solution of the chloroform-insoluble fraction of the product in 50% aqueous ethanol deposited the *7-methylquinolinium benzenesulphonate* (17·6 g., 27%) as elongated prisms, m. p. 289—291° (decomp.) (Found: C, 57·9; H, 4·8; N, 8·3. $C_{16}H_{16}O_4N_2S$ requires C, 57·8; H, 4·9; N, 8·4%). The free *base* occurred as solvated needles (from aqueous ethanol), m. p. 331° (decomp.) (Found: C, 69·4; H, 5·3; N, 15·8. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%); its *picrate*, needles from propan-2-ol, had m. p. 275—276° (decomp.) (Found: N, 17·1. $C_{16}H_{13}O_8N_5$ requires N, 17·4%).

On being concentrated, the aqueous ethanolic mother-liquor furnished the *benzenesulphonate* (19·6 g., 15%) of the 5-methyl isomer, which crystallised from propan-2-ol as prisms, m. p. 274—275° (decomp.) (Found: C, 57·8; H, 4·7; N, 8·5. $C_{16}H_{16}O_4N_2S$ requires C, 57·8; H, 4·9; N, 8·4%). *2-Amino-4-hydroxy-5-methylquinoline* crystallised as solvated needles, m. p. 283—284° (decomp.), from aqueous ethanol (Found: C, 69·1; H, 5·4; N, 15·8. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%); its *picrate*, needles, m. p. 258—259° (decomp.), crystallised from aqueous ethanol (Found: C, 48·1; H, 3·7; N, 17·4. $C_{16}H_{12}O_8N_5$ requires C, 47·7; H, 3·3; N, 17·4%).

*2-Amino-3-bromo-4-hydroxy-7-methylquinoline.*—2-Amino-4-hydroxy-7-methylquinoline (19·6 g.), treated in boiling glacial acetic acid (300 ml.) with bromine (18 g.), gave the *3-bromo-hydrobromide* (36·5 g., 97%), which crystallised from glacial acetic acid as needles, m. p. 221—222° (decomp.) (Found: C, 35·8; H, 3·5. $C_{10}H_{10}ON_2Br_2$ requires C, 36·0; H, 3·0%). The *base* crystallised from aqueous ethanol as needles, m. p. 285° (decomp.) (Found: C, 47·8; H, 3·6; N, 10·8. $C_{10}H_9ON_2Br$ requires C, 47·3; H, 3·6; N, 11·0%); its *picrate*, needles from aqueous ethanol, had m. p. 238—239° (decomp.) (Found: N, 14·5. $C_{16}H_{12}O_8N_5Br$ requires N, 14·5%).

*3-Bromo-2 : 4-dihydroxy-7-methylquinoline.*—Sodium nitrite (24 g.) was gradually stirred into a solution of 2-amino-3-bromo-4-hydroxy-7-methylquinoline (25 g.) in concentrated sulphuric acid (63 ml.) at 0°. Next day, the paste was treated with crushed ice, and the

[11] Friedländer and Weinberg, *Ber.*, 1882, **15**, 2679.

XUM

precipitate was collected. Crystallisation of the ethanol-soluble fraction from glacial acetic acid gave the 2 : 4-*dihydroxy-derivative* (14·4 g., 57%) as plates, m. p. 254—255° (decomp.) (Found: C, 47·0; H, 3·2; N, 5·4. $C_{10}H_8O_2NBr$ requires C, 47·1; H, 3·2; N, 5·5%). On acetylation with acetic anhydride and a trace of pyridine, this dihydroxyquinoline gave a *monoacetate*, needles, m. p. 242° (decomp.) (from ethanol) (Found: C, 48·9; H, 3·6; N, 4·6. $C_{12}H_{10}O_3NBr$ requires C, 48·7; H, 3·4; N, 4·7%).

2 : 4-*Dihydroxy-7-methylquinoline* was obtained (89%) by reduction of the foregoing 3-bromoquinoline (10·4 g.) in 10% aqueous sodium hydroxide (300 ml.) with Raney alloy (38 g.) at 90° and crystallised from glacial acetic acid as prisms, m. p. above 400° (Found: C, 68·7; H, 5·3; N, 7·9. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·2; N, 8·0%). Its *monoacetate*, needles from ethanol, had m. p. 229—230° (decomp.) (Found: C, 66·0; H, 4·8; N, 6·5. $C_{12}H_{11}O_3N$ requires C, 66·4; H, 5·1; N, 6·5%).

2 : 4-*Dichloro-7-methylquinoline* was produced (6·4 g.) when the dihydroxymethylquinoline (5·5 g.) was boiled with phosphorus oxychloride (25 ml.) for 7 hr. and the mixture was worked up in the usual way; it formed needles, m. p. 107—108°, from methanol (Found: N, 6·7; Cl, 34·1. $C_{10}H_7NCl_2$ requires N, 6·6; Cl, 33·4%).

1 : 2 : 3 : 4-*Tetrahydro-7-methylquinoline* was obtained (73%) from the foregoing 2 : 4-dichloroquinoline by reduction with tin and hydrochloric acid [6] and characterised by comparison of its benzoyl derivative, m. p. 77—78°, its hydrochloride, m. p. 204—205°, and its picrate, m. p. 156°, with authentic specimens. For this comparison, 7-methylquinoline (12 g.) in ethanol (300 ml.) and 10% aqueous sodium hydroxide (300 ml.) was reduced at the b. p. during 4 hr. with Raney alloy (35 g.). The tetrahydro-derivative (78%) furnished a picrate, m. p. 154—155° (decomp.), previously reported [12] to have m. p. 153—154°. The hydrochloride, prisms, m. p. 204—205°, from methanol–ethyl acetate, was prepared from the picrate (Found: C, 65·6; H, 7·8; N, 7·6. Calc. for $C_{10}H_{14}NCl$: C, 65·4; H, 7·7; N, 7·6%); the benzoyl derivative, prepared from the hydrochloride, crystallised from light petroleum as prisms, m. p. 77—78° (Found: C, 81·2; H, 6·9; N, 5·5. Calc. for $C_{17}H_{17}ON$: C, 81·2; H, 6·8; N, 5·6%). Previously reported [12] values for these m. p.s are 175° and 70—72° respectively. The 7-methylquinoline was authenticated [13] as its picrate, m. p. 242°, and styphnate, m. p. 242°.

2-*Amino-4-hydroxy-7-methoxyquinoline*.—The *benzenesulphonate* of this base separated from a chloroform solution of the product of interaction of *m*-methoxyanilinium benzenesulphonate and ethyl cyanoacetate (1 mol.) at 210° for 1 hr.; it afforded solvated prisms, m. p. 222°, from water (Found: C, 55·4; H, 4·2; N, 8·2. $C_{16}H_{16}O_5N_2S$ requires C, 55·2; H, 4·6; N, 8·0%); yield 39%. The *base*, prisms from aqueous ethanol, had m. p. 309—310° (decomp.) (Found: C, 62·8; H, 5·1; N, 14·4. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%). Its 3-*bromo-derivative*, prepared in the usual way, crystallised as needles, m. p. 283° (decomp.), from aqueous lactic acid (Found: C, 44·9; H, 3·7; N, 10·4. $C_{10}H_9O_2N_2Br$ requires C, 44·6; H, 3·4; N, 10·4%) and gave a *hydrobromide* as needles, m. p. 231—232° (decomp.), from glacial acetic acid (Found: C, 34·1; H, 3·1; N, 8·0. $C_{10}H_{10}O_2N_2Br_2$ requires C, 34·3; H, 2·9; N, 8·0%).

2-*Amino-4-chloro-7-methoxyquinoline*.—2-Amino-4-hydroxy-7-methoxyquinoline (30·5 g.) was boiled with phosphorus oxychloride (150 ml.) for 8 hr. The solid obtained by evaporation, when boiled for 90 min. with 25% aqueous hydrochloric acid (300 ml.), gave the *hydrochloride* which crystallised as solvated prisms, m. p. 210° (decomp.), from dilute hydrochloric acid (Found: C, 48·8; H, 4·3; N, 11·4; Cl, 28·2. $C_{10}H_{10}ON_2Cl_2$ requires C, 49·0; H, 4·1; N, 11·4; Cl, 28·9%). On basification, this salt furnished the *chloroquinoline* (28 g., 87%), prisms (from benzene), m. p. 200° (Found: C, 57·8; H, 4·3; N, 13·4; Cl, 16·7. $C_{10}H_9ON_2Cl$ requires C, 57·5; H, 4·4; N, 13·4; Cl, 17·0%). This compound could not be brought into reaction with aniline. Its *picrate*, dark red prisms from 2-ethoxyethanol, had m. p. 270° (decomp.) (Found: C, 43·7; H, 2·9; Cl, 7·6. $C_{16}H_{12}O_8N_5Cl$ requires C, 43·9; H, 2·8; Cl, 8·1%).

4-*Chloro-2-hydroxy-7-methoxyquinoline*.—The foregoing 2-amino-derivative (10 g.) in ice-cold, concentrated sulphuric acid (30 ml.) was treated with sodium nitrite (10 g.). Next day, the mixture, when added to crushed ice, furnished 4-*chloro-2-hydroxy-7-methoxyquinoline* (68%) which crystallised from ethanol as needles, m. p. 252° (Found: C, 57·3; H, 3·6; N, 6·6. $C_{10}H_8O_2NCl$ requires C, 57·3; H, 3·8; N, 6·7%).

2 : 4-*Dichloro-7-methoxyquinoline* was produced (95%) when 4-chloro-2-hydroxy-7-methoxyquinoline was boiled with phosphorus oxychloride for 16 hr.; it formed needles, m. p. 132—133°,

[12] von Braun, Gmelin, and Schultheiss, *Ber.*, 1923, **56**, 1338.
[13] Bradford, Elliott, and Rowe, *J.*, 1947, 437.

from ethanol (Found: C, 52·6; H, 3·1; Cl, 30·9. $C_{10}H_7ONCl_2$ requires C, 52·7; H, 3·1; Cl, 31·1%).

1 : 2 : 3 : 4-*Tetrahydro-7-methoxyquinoline.*—(i) 7-Methoxyquinoline (10·3 g.) was heated on a steam-bath for 21 hr. with tin (50 g.) and concentrated hydrochloric acid (130 ml.). Excess of alkali was added; the steam-volatile material, after isolation and fractionation, afforded 1 : 2 : 3 : 4-*tetrahydro-7-methoxyquinoline* (3·4 g., 32%), b. p. 127—128°/1·8 mm. (Found: C, 73·7; H, 7·9; N, 8·7. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0; N, 8·6%). Its *benzoyl derivative* crystallised from light petroleum (b. p. 40—60°) as prisms, m. p. 81—82° (Found: C, 76·4; H, 6·3; N, 5·4. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4; N, 5·2%), its *hydrochloride* as prisms, m. p. 181°, from methanol–ethyl acetate (Found: C, 60·2; H, 6·6. $C_{10}H_{14}ONCl$ requires C, 60·1; H, 7·1%), and its *picrate* as rods, m. p. 156° (decomp.), from ethanol (Found: C, 48·9; H, 4·2; N, 14·2. $C_{16}H_{16}O_8N_4$ requires C, 49·0; H, 4·1; N, 14·3%). The non-volatile material was collected in ether and recovered; its basic fraction, after being extracted with acid and reprecipitated, gave on fractional crystallisation from benzene–light petroleum a less-soluble *substance* as solvated prisms, m. p. 170—178° [Found: C, 74·8; H, 7·0; N, 8·1%; *M* (Rast), 657. $C_{40}H_{48}O_4N_4$ requires C, 74·3; H, 7·2; N, 8·7%; *M*, 646], and a more-soluble *substance* as prisms, m. p. 99—107° [Found: C, 74·5; H, 7·3; N, 8·2%; *M* (Rast), 326. $C_{20}H_{24}O_2N_2$ requires C, 74·0; H, 7·5; N, 8·6%; *M*, 324]. Both these compounds gave, after treatment with nitrous acid, a positive Liebermann's test.

The 7-methoxyquinoline was characterised as its picrate, m. p. 234—235°, oxalate, m. p. 120°, and dichromate, m. p. 203°. Bradford, Elliott, and Rowe [13] record m. p. 229°, 126°, and 210° respectively for these salts.

(ii) 2 : 4-Dichloro-7-methoxyquinoline, reduced by the same method, furnished the same tetrahydromethoxyquinoline in 35% yield, the identity being confirmed by the m. p. and mixed m. p. of the benzoyl derivatives, hydrochlorides, and picrates.

2-*Amino*-4 : 7-*dihydroxyquinoline.*—(i) The product of interaction of *m*-hydroxyanilinium benzenesulphonate (53·4 g.) and ethyl cyanoacetate (22·6 g.) at 210° for 1 hr., on prolonged digestion with acetone, gave a solid which, after basification, removal of ethanol-soluble impurities, purification *via* its hydrochloride, and crystallisation from ethanol afforded 2-*amino*-4 : 7-*dihydroxyquinoline* (9·4 g., 27%) as solvated prisms, m. p. 400—401° (decomp.) (Found: C, 61·2; H, 4·5; N, 16·1. $C_9H_8O_2N_2$ requires C, 61·4; H, 4·6; N, 15·9%). Its *hydrochloride* formed solvated needles, m. p. 297—298° (decomp.), from dilute hydrochloric acid (Found: C, 50·9; H, 4·6; N, 12·7. $C_9H_9O_2N_2Cl$ requires C, 50·9; H, 4·3; N, 13·2%) and its *picrate*, solvated prisms from aqueous ethanol, had m. p. 283° (decomp.) (Found: C, 44·6; H, 2·8. $C_{15}H_{11}O_9N_5$ requires C, 44·5; H, 2·7%).

(ii) 2-Amino-4-hydroxy-7-methoxyquinoline was boiled for 10 hr. with 55% hydriodic acid; from the reaction mixture there was recovered a base (91%), m. p. 400—401° (decomp.), which yielded a hydrochloride, m. p. 297—298° (decomp.), and a picrate, m. p. 283° (decomp.), all undepressed on appropriate admixture with the foregoing compounds.

2-Amino-4-chloro-7-hydroxyquinoline was obtained (97%) as its *hydrochloride* when 2-amino-4 : 7-dihydroxyquinoline was boiled with phosphorus oxychloride for 11 hr. and the mixture was worked up as described for the corresponding 7-methoxyquinoline; it crystallised as solvated prisms, m. p. 282—283° (decomp.), from dilute hydrochloric acid (Found: C, 47·1; H, 3·7; N, 12·3; Cl, 30·9. $C_9H_8ON_2Cl_2$ requires C, 46·8; H, 3·5; N, 12·1; Cl, 30·7%); the *base* formed solvated prisms, m. p. 226°, from aqueous ethanol (Found: N, 14·3; Cl, 17·5. $C_9H_7ON_2Cl$ requires N, 14·4; Cl, 18·2%), the *benzenesulphonate* prisms, m. p. 209—210°, from propan-2-ol (Found: C, 50·7; H, 3·6; N, 7·5; Cl, 10·1. $C_{15}H_{13}O_4N_2ClS$ requires C, 51·1; H, 3·7; N, 7·9; Cl, 10·1%), and the *picrate* prisms, m. p. 290—291° (decomp.), from aqueous ethanol (Found: N, 16·4; Cl, 8·4. $C_{15}H_{10}O_9N_5Cl$ requires N, 16·5; Cl, 8·4%).

The same base was obtained (*ca.* 100%) when 2-amino-4-chloro-7-methoxyquinoline was boiled with constant-boiling hydriodic acid for 8 hr. and the mixture was basified. The identity was confirmed by comparison of the hydrochlorides and picrates.

When 2-amino-4-chloro-7-hydroxyquinoline was boiled for 10 hr. with 20% potassium hydroxide in ethylene glycol, 2-amino-4 : 7-dihydroxyquinoline (57%) was produced.

2-*Amino*-5- *and* -7-*chloro*-4-*hydroxyquinoline.*—The cooled melt obtained after heating together *m*-chloroanilinium benzenesulphonate (129 g.) and ethyl cyanoacetate (51 g.) for 90 min. at 210° was digested with chloroform for 24 hr. 2-*Amino*-7-*chloro*-4-*hydroxyquinolinium benzenesulphonate* (35 g., 22%) which separated from the cold solution gave prisms, m. p.

XUM

272—273°, after recrystallisation from aqueous ethanol (Found: C, 51·2; H, 3·5; N, 7·3. $C_{18}H_{13}O_4N_2ClS$ requires C, 51·1; H, 3·7; N, 7·9%); the *base* formed rods, m. p. 348—349° (decomp.), from aqueous ethanol (Found: C, 55·9; H, 3·8. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6%), and the *picrate* prisms, m. p. 290—291° (decomp.), from aqueous ethanol (Found: N, 16·2. $C_{15}H_{10}O_8N_5Cl$ requires N, 16·5%). At 5°, the chloroform mother-liquor deposited *2-amino-5-chloro-4-hydroxyquinolinium benzenesulphonate* (7 g., 4%) which crystallised from aqueous ethanol as prisms, m. p. 280° (decomp.), depressed to 240—252° by the 7-isomer (Found: C, 51·3; H, 3·6; N, 8·3. $C_{18}H_{13}O_4N_2ClS$ requires C, 51·1; H, 3·7; N, 7·9%); this yielded the *base*, plates (from aqueous ethanol), m. p. 352—353° (decomp.), depressed to 310—313° (decomp.) by the 7-isomer (Found: C, 55·4; H, 3·7; N, 14·1. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6; N, 14·4%), and *picrate*, needles, m. p. 243—244° (decomp.), from aqueous ethanol (Found: C, 42·8; H, 2·8. $C_{15}H_{10}O_8N_5Cl$ requires C, 42·5; H, 2·4%).

*7-Chloro-3 : 4-dihydro-2-hydroxy-3-hydroxyimino-4-oxoquinoline.*—Sodium nitrite (5 g.) was gradually stirred into a solution of 2-amino-7-chloro-4-hydroxyquinoline (4·9 g.) in concentrated sulphuric acid (22 ml.) at 0°. Next day, the paste was mixed with ice. The glacial acetic acid-soluble fraction of the precipitated material afforded with sodium hydroxide a green sodium salt which, after decomposition with dilute hydrochloric acid and crystallisation from glacial acetic acid, gave the required *2-hydroxy-3-hydroxyimino-derivative* as green-yellow prisms, m. p. 233° (decomp.) (2·7 g., 48%) (Found: C, 48·1; H, 2·4; N, 12·3; Cl, 15·1. $C_9H_5O_3N_2Cl$ requires C, 48·1; H, 2·2; N, 12·5; Cl, 15·8%).

*6-Chloroisatin.*—The foregoing oxoquinoline (1·8 g.) when boiled with 30% sulphuric acid (70 ml.) for 1 hr. furnished 6-chloroisatin (1·1 g., 75%) which crystallised from dilute sulphuric acid as orange prisms, m. p. 256·5—258°; Senear *et al.*[14] record m. p. 258—259° (Found: C, 52·4; H, 2·4; N, 8·0. Calc. for $C_8H_4O_2NCl$: C, 52·9; H, 2·2; N, 7·7%). On oxidation with hydrogen peroxide,[15] this isatin gave 4-chloroanthranilic acid,[16] m. p. and mixed m. p. 236—237° (decomp.); reduction of the diazonium salt derived from this amine with hypophosphorous acid furnished *p*-chlorobenzoic acid, m. p. and mixed m. p. 242—243°.

2-Amino-4 : 7-dichloroquinoline was prepared (81%) as its *hydrochloride* from 2-amino-7-chloro-4-hydroxyquinoline and phosphorus oxychloride and formed needles, m. p. 246·5—247·5°, from dilute hydrochloric acid (Found: C, 43·5; H, 3·1; N, 11·5. $C_9H_7N_2Cl_3$ requires C, 43·3; H, 2·8; N, 11·2%); this afforded the *base*, needles, m. p. 201—202°, from benzene (Found: N, 13·5; Cl, 33·6. $C_9H_6N_2Cl_2$ requires N, 13·2; Cl, 33·3%), and *picrate*, needles, m. p. 285—286° (decomp.), from glacial acetic acid (Found: C, 40·8; H, 2·0; N, 15·5; Cl, 16·4. $C_{15}H_9O_7N_5Cl_2$ requires C, 40·7; H, 2·1; N, 15·8; Cl, 16·0%). The hydroxyl group in 2-amino-4-chloro-7-hydroxyquinoline was not attacked by phosphorus oxychloride, phosphorus pentachloride, and cetyltrimethylammonium bromide.[17]

The authors gratefully acknowledge their indebtedness to Mr. E. C. Wilmshurst and Miss M. E. Thompson, Boots Pure Drug Co., Ltd., for the biological tests.

THE UNIVERSITY, NOTTINGHAM. [*Received, August 13th*, 1957.]

[14] Senear, Sargent, Mead, and Koepfli, *J. Amer. Chem. Soc.*, 1946, **68**, 2695.
[15] Mayer and Schulze, *Ber.*, 1925, **58**, 1465.
[16] Cohn, *Monatsh.*, 1901, **22**, 473.
[17] Cairns and Kermack, *J.*, 1950, 1322.

# 121. *Physical Properties of the Lower Dialkyl Hydrogen Phosphites.*

By F. M. Page and J. H. Purnell.

The vapour pressures and latent heats of dimethyl, diethyl, di-*n*-propyl and di-*n*-butyl hydrogen phosphites have been measured over a wide range of temperature. Cryoscopic measurements both in benzene and in camphor have been carried out. The results suggest that the dimethyl, and to a lesser extent, the diethyl ester are associated in the liquid phase. Higher members of the series, however, are monomeric.

Although dialkyl phosphites have recently become increasingly important as organic intermediates, there is very little information about their physical properties in the literature. For a long time the chief interest lay in their constitution and the valency of the phosphorus atom. More recently, there has been considerable discussion, notably between the schools of Arbuzov and Kosolapoff, as to whether these substances were dimeric in the liquid phase. We have determined the vapour pressures and studied relatively dilute solutions of the lower members of the series cryoscopically in benzene and camphor, and conclude that dimerization, although occurring in dimethyl and diethyl phosphites, is not as important as has been suggested.

## Experimental and Results.

*Vapour Pressures.*—The vapour pressures of dimethyl, diethyl, di-*n*-propyl and di-*n*-butyl hydrogen phosphites were determined by conventional manometry. The manometer and bulb, after being sealed off on a vacuum line, were completely immersed in a paraffin-oil bath. The pressures observed were corrected for expansion of mercury. The results (Fig. 1) can be represented by the equation

$$\log_{10} p_{mm} = A - B/T$$

The constants $A$ and $B$, the latent heat of vaporisation, the computed boiling point at 1 atm., and Trouton's constant are given in the Table. The estimated accuracy of the latent heat is $\pm 0{\cdot}1$ kcal./mole and that of the boiling points $\pm 2°$.

| Hydrogen phosphite | $A$ | $B$ | Latent heat (kcal./mole) | B. p. | Trouton's constant |
|---|---|---|---|---|---|
| Dimethyl | 7·439 | 2·0226 | 9·25 | 170·6° | 20·8 |
| Diethyl | 7·174 | 1·9885 | 9·10 | 190·0 | 19·6 |
| Di-*n*-propyl | 7·062 | 1·9911 | 9·11 | 203·0 | 19·1 |
| Di-*n*-butyl | 6·800 | 1·9732 | 9·03 | 230·3 | 17·9 |

Samples were obtained from two sources. Dimethyl and diethyl hydrogen phosphites supplied by Messrs. Albright and Wilson were redistilled under vacuum and samples of the diethyl, di-*n*-propyl, and di-*n*-butyl esters were kindly supplied by Dr. V. M. Clark. The agreement between the results obtained with the two specimens of diethyl hydrogen phosphite was satisfactory. Infrared analysis, carried out by Dr. Clark, showed that even after redistillation there were still residual traces of free alcohol.

*Cryoscopy.*—The freezing points of a series of solutions of the phosphites in benzene were determined in a conventional Beckmann apparatus. The accuracy required to demonstrate the presence of dimerised molecules was well within that of the technique without special precautions. A further series of experiments was carried out with camphor as solvent. The melting points of the solutions were measured on a heated-stage microscope. The results of these two series of experiments are shown in Figs. 2 and 3, where the depression of freezing point, $\Delta T$, is plotted against the mole fraction of solute computed from the monomeric molecular weight.

XUM

## Discussion

Data relating to the vapour pressures and boiling points are few, being restricted almost entirely to observations of the conditions of distillation, and refer to pressures of the order of magnitude of 1 cm. of mercury. The isolated observations of the boiling point at 1 atm. are in reasonable agreement with those presented here; for example, the normal boiling point of the diethyl ester is given [1] as 186·7°.

The unexpectedly low latent heats suggest that dimerization may occur in the vapour phase. Consequently, we tried to measure the vapour density of the dimethyl ester by

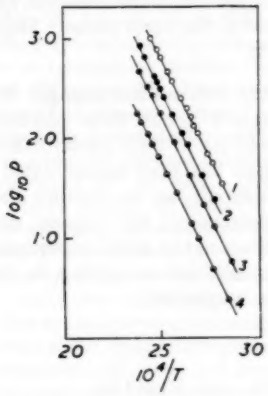



Fig. 1. *Vapour pressures.*

Fig. 2. *Freezing-point depression in benzene.*

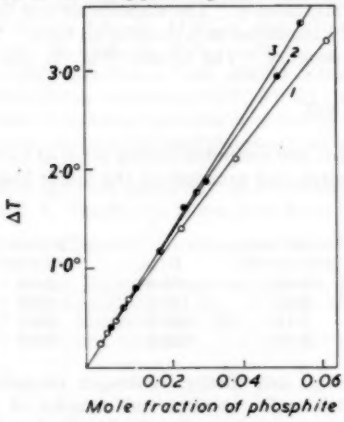
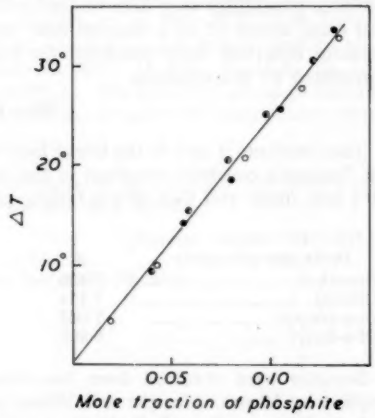



Fig. 3. *Freezing-point depression in camphor.*




*Key for all Figs.*—1, ○ Dimethyl, 2, ● diethyl, 3, ◐ di-*n*-propyl, 4, ◒ di-*n*-butyl hydrogen phosphite.

Dumas's method, but the experimental difficulties precluded a definite answer. The measured value was consistent with a monomeric form. However, this finding can only be taken to show that, 30° above the normal boiling point, the extent of dimerization is not great.

One of the easier methods of detection of hydrogen bonding would be a study of the infrared spectra. However, what results have been thus obtained are in conflict. Meyrick

[1] A. E. Arbuzov, *Ber.*, 1905, **38**, 1171.

and Thompson [2] find evidence for association in the liquid phase while Bellamy and Beecher [3] do not. Arbuzov, Batuev, and Vinogradova [4] obtained evidence from the Raman spectra which supported the view that there was considerable dimerization. Arbuzov and Vinogradova [5] measured the parachors of the dialkyl hydrogen phosphites and claimed to demonstrate dimerization in members of the series as high as dioctyl, though later [6] they modified this statement by suggesting that members above dipentyl were largely monomeric. They supported this by cryoscopy in benzene, which apparently showed that dimethyl hydrogen phosphite, for example, was monomeric only in highly dilute solution. This view was contradicted by Kosolapoff and Powell who studied freezing points in naphthalene [7] and benzene solutions,[8] claiming to demonstrate that the diethyl and di-*n*-butyl esters were monomeric, and that an acidic hydroxyl group was necessary for dimerization. Finally, Arbuzov and Vinogradova,[9] who studied viscosities of solutions in carbon tetrachloride and benzene, suggested that the esters including and above di-*n*-butyl were monomeric, lower members being dimeric.

The cryoscopic evidence now obtained substantiates the general claims of Arbuzov *et al.* that dimethyl and diethyl hydrogen phosphites appear to be partially dimerized in benzene solution. However, Kosolapoff and Powell's measurements are not inconsistent with this. They presented their results as experimental molecular weights without any statement of experimental conditions. These molecular weights were slightly higher than those calculated for the monomeric form. We present our results as the lowering of freezing point, a form which enables divergencies from ideal behaviour to become more apparent. Fig. 2 shows clearly that at mole fractions higher than about 0·02 the dimethyl ester is increasingly associated but the extent of association is only about 13% at mole fraction 0·05. If this result can be extrapolated to 100% of the phosphite this would correspond to about 75% dimerization. The divergence of the diethyl ester from ideality is considerably less and none at all was observed for the di-*n*-propyl in the concentration range examined.

Turning to the measurements at higher temperatures we find that, within experimental error, the freezing-point depression of camphor for all three esters could be represented by a simple straight line when plotted on a mole-fraction basis. This line lay very slightly below the line obtained for naphthalene in camphor but the difference was scarcely more than experimental error and since the difference was common to all the esters it appears to be an activity effect.

We conclude that dimethyl and diethyl hydrogen phosphites are associated at normal temperatures but that the extent of dimerization of the latter is relatively small. Further, there is no evidence of association in solution above about 150° for any of the esters and it is, therefore, unlikely that the vapours should contain significant amounts of dimeric molecules. Thus the low and gradually decreasing Trouton constant with increasing molecular weight probably does not indicate the formation of definite dimers.

DEPARTMENT OF PHYSICAL CHEMISTRY, CAMBRIDGE. [*Received, August 26th*, 1957.]

[2] Meyrick and Thompson, *J.*, 1950, 225.
[3] Bellamy and Beecher, *J.*, 1952, 475.
[4] A. E. Arbuzov, Batuev, and Vinogradova, *Doklady Akad. Nauk S.S.S.R.*, 1946, **54**, 599.
[5] B. A. Arbuzov and Vinogradova, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1947, 459.
[6] *Idem, Doklady Akad. Nauk S.S.S.R.*, 1950, **72**, 695.
[7] Kosolapoff and Powell, *J.*, 1950, 3535.
[8] *Idem, J. Amer. Chem. Soc.*, 1950, **72**, 4291.
[9] B. A. Arbuzov and Vinogradova, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1952, 507.

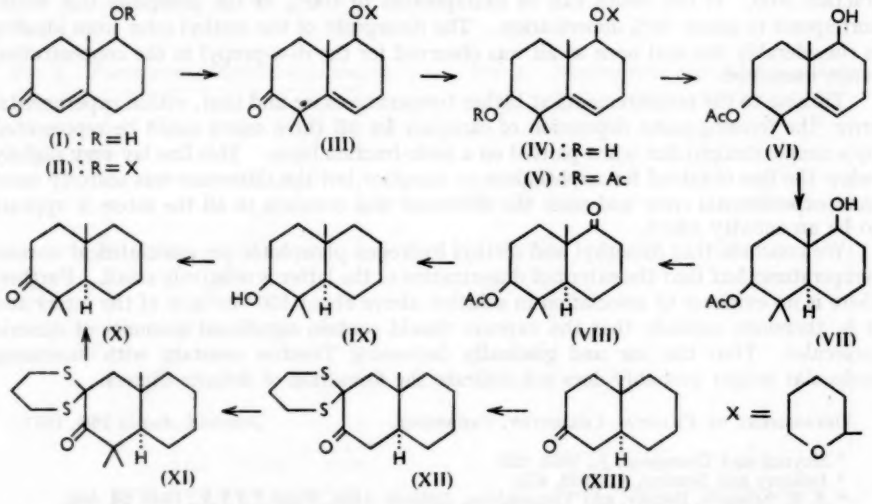
## 122. *Studies in the Synthesis of Terpenes. Part III.* The Synthesis of* 6-*Acetoxy*-5 : 5 : 9-*trimethyl*-trans-*decal*-1-*one.*

By B. Gaspert, T. G. Halsall, and D. Willis.

The conversion of 5-hydroxy-10-methyl-$\Delta^{1(9)}$-octal-2-one (I) into 6-acetoxy-5 : 5 : 9-trimethyl-*trans*-decal-1-one (VIII) is described. The *trans*-nature of the ring fusion has been proved by conversion of the decalone (VIII) into 1 : 1 : 10-trimethyl-*trans*-decal-2-one (X) which has been synthesised from 10-methyl-*trans*-decal-2-one (XIII).

In our studies of terpene synthesis 6-acetoxy-5 : 5 : 9-trimethyl-*trans*-decal-1-one (VIII) has been prepared. This compound, which has the characteristic 3-oxygen atom of triterpenes, could be used in the synthesis of derivatives of onocerin [1] and, possibly, pentacyclic triterpenes. What is probably the benzoate corresponding to the acetate (VIII), although the *trans*-fusion of its rings has not been proved, has been prepared by King, Ritchie, and Timmons [2] by a route different from that described below.

5-Hydroxy-10-methyl-$\Delta^{1(9)}$-octal-2-one [3,4,5] (I) was converted into its tetrahydropyranyl ether (II) by a slightly different procedure from that previously described.[3] Again the ether, as normally obtained, melted over a range suggesting the presence of two stereoisomers involving the 2-position of the tetrahydropyran ring. Repeated recrystallisation afforded crystals melting over only 1° and so presumably of one stereoisomer, but the mixture of the two isomers was satisfactory for further use.




The tetrahydropyranyl ether (II) was methylated by the method of Woodward *et al.*[6,7] to give the trimethyloctalone (III) with the protective grouping still intact. This with lithium aluminium hydride gave the octalin-2-ol (IV) which was converted into the acetyl

* Part II, *J.*, 1957, 3441.

[1] Cf. Elad and Sondheimer, *Proc. Chem. Soc.*, 1957, 206.
[2] King, Ritchie, and Timmons, *Chem. and Ind.*, 1956, 1230.
[3] Cocker and Halsall, *J.*, 1957, 3441; *Chem. and Ind.*, 1956, 1275.
[4] Elad and Sondheimer, *Bull. Res. Council Israel*, 1956, **5**, *A*, 269; *J. Amer. Chem. Soc.*, 1957, **79**, 5542.
[5] Birch, Quartey, and Smith, *J.*, 1950, 1768.
[6] Woodward, Patchett, Barton, Ives, and Kelly, *J. Amer. Chem. Soc.*, 1954, **76**, 2852.
[7] *Idem*, *J.*, 1957, 1131.

derivative (V) under conditions which did not lead to loss of the ether group. The octalone (III) and the hydroxyoctalin (IV) were obtained as oils, probably again because of the presence of two stereoisomers as above. The octalone was, however, converted into a solid semicarbazone. The acetyl derivative (V) was crystalline: as first obtained it melted over a range, but recrystallisation gave sharply melting prisms, presumably of one isomer. After removal of the protective grouping, the cause of this isomerism disappears and the subsequent compounds were readily obtained as sharply melting crystals.

The ether grouping of compound (V) was removed and the resulting monoacetate (VI) hydrogenated with a platinum catalyst in acetic acid to give the *trans*-monoacetate (VII). That the hydrogenation had given the *trans*- rather than the *cis*-decalin derivative follows from the experiments described below. The monoacetate (VII) was oxidised with chromic acid to 6-acetoxy-5 : 5 : 9-trimethyl-*trans*-decal-1-one (VIII). This was reduced (Wolff–Kishner) to the alcohol (IX) which was oxidised to 1 : 1 : 10-trimethyl-*trans*-decal-2-one (X) identical with an authentic sample prepared as follows.

10-Methyl-*trans*-decal-2-one (XIII) was prepared from 10-methyl-$\Delta^{1(9)}$-octal-2-one,[8] obtained by an improved procedure, by lithium–ammonia reduction which is known to lead to the *trans*-ring fusion.[9] Its 2 : 4-dinitrophenylhydrazone had the melting point reported by Woodward *et al.*[10] The $C_{(3)}$ position of the decalone (XIII) was blocked by the introduction of a thioketal grouping by the method devised by Woodward *et al.*[7] Two methyl groups were then introduced at position 1 by means of methyl iodide and sodium *tert.*-amyloxide in benzene. The carbonyl stretching band in the infrared spectrum (in $CCl_4$) of the resulting trimethyldecalone (XI) was at a frequency (1692 cm.$^{-1}$) somewhat lower than is usual for a carbonyl group in a saturated six-membered ring, in agreement with that found for 4 : 4-dimethyl-3-oxocholestane-2-*spiro*-2′-(1′ : 3′-dithian) (C=O frequency at 1686 cm.$^{-1}$)[11] where there is also a carbonyl group in a saturated six-membered ring flanked by two methyl groups and the thioketal group. The thioketal group was finally removed by use of deactivated Raney nickel, to give 1 : 1 : 10-trimethyl-*trans*-decal-2-one (X) identical with that obtained from the acetyl derivative (VIII).

Wolff–Kishner reduction of the decalone (X) gave 1 : 1 : 10-trimethyl-*trans*-decalin which was identical with the Wolff–Kishner reduction product of the 5 : 5 : 9-trimethyldecal-1-one[3,4] previously described. This proves that this decalone has a *trans*-ring junction. Previously this had been only assumed.

## Experimental

M. p.s were determined on a Kofler block and are corrected. The alumina used was neutral; it was prepared by neutralising Peter Spence " Grade H " alumina with 0·5N-hydrochloric acid, washing it with boiling water, and activating it at 140° for 12 hr. under reduced pressure. Light petroleum refers to the fraction with b. p. 60—80°, unless otherwise stated.

*10-Methyl-5-tetrahydropyranyloxy-*$\Delta^{1(9)}$*-octal-2-one* (II).—5-Hydroxy-10-methyl-$\Delta^{1(9)}$-octal-2-one monohydrate[3] (20 g.) was dried over phosphoric oxide at 50—55°/20 mm. for 15 min. and then for 10 min. in a high vacuum. The oily residue (18 g.) in dihydropyran (60 c.c.; redistilled from potassium hydroxide) was treated with a 1·6% solution of hydrogen chloride in dry ether (2 c.c.) and kept overnight. Ether (40 c.c.) was added and the solution washed with sodium hydrogen carbonate solution and water, dried, and evaporated under reduced pressure to an oil which was dissolved in light petroleum and kept overnight at −5°. The ether (13·9 g.) separated as prisms, m. p. 55—65°. Further recrystallisation from light petroleum gave prisms, m. p. 82—83° (Found: C, 73·0; H, 8·9. Calc. for $C_{16}H_{24}O_3$: C, 72·7; H, 9·15%), $\lambda_{max.}$ 2375 Å (ε 15,300), $\nu_{max.}$ (in $CCl_4$) 1675, 1075, and 1055 (C·O·C·O·C), and 1030 cm.$^{-1}$ (ether linkage).

*1 : 1 : 10-Trimethyl-5-tetrahydropyranyloxy-*$\Delta^{8}$*-octal-2-one* (III).—10-Methyl-5-tetrahydropyranyloxy-$\Delta^{1(9)}$-octal-2-one (2 g.) in *tert.*-butyl alcohol (32 c.c.) at 40° was treated with

[8] Du Feu, McQuillin, and Robinson, *J.*, 1937, 53.
[9] Barton and Robinson, *J.*, 1954, 3045.
[10] Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.
[11] Beton, Halsall, Jones, and Phillips, *J.*, 1953, 753.

potassium *tert.*-butoxide (0·88 g. of potassium) in the same solvent (20 c.c.). Methyl iodide (6·4 g.) in dry *tert.*-butyl alcohol (6 c.c.) was immediately added and the mixture was heated under reflux for 1 hr. under nitrogen. Evaporation under reduced pressure, dilution with water, and extraction with ether afforded an oil (2·04 g.) which was taken up in light petroleum and filtered through alumina along with light petroleum (100 c.c.). The resultant oil (1·75 g.) was further chromatographed on alumina (30 g.), to give 1 : 1 : 10-*trimethyl-5-tetrahydropyranyloxy-*$\Delta^8$*-octal-2-one* as an oil (1·3 g., 62%). An analytical sample had $n_D^{15}$ 1·5112 (Found: C, 74·3; H, 9·9. $C_{18}H_{28}O_3$ requires C, 73·9; H, 9·65%), $\nu_{max.}$ ($CCl_4$) 1720 (saturated ketone), 1385 and 1360 (*gem.*-dimethyl), and 1076, 1065, and 1032 cm.$^{-1}$ (C·O·C·O·C). The *semicarbazone* crystallised from ethanol as stout needles, m. p. 204—207° (Found: C, 65·15; H, 8·75; N, 12·3. $C_{19}H_{31}O_3N_3$ requires C, 65·3; H, 8·95; N, 12·0%).

2-*Acetoxy*-1 : 1 : 10-*trimethyl-5-tetrahydropyranyloxy-*$\Delta^8$*-octalin* (V).—1 : 1 : 10-Trimethyl-5-tetrahydropyranyloxy-$\Delta^8$-octal-2-one (5·3 g.) in ether (400 c.c.) was added during 45 min. to a stirred solution of lithium aluminium hydride (1·3 g.) in ether (150 c.c.), heated under reflux. Half of the solvent was then removed under reduced pressure, an equal volume of water was added, and the mixture centrifuged. The resulting ether layer, free from colloidal aluminium salts, was washed with water, dried, and evaporated, to give 1 : 1 : 10-trimethyl-5-tetrahydropyranyloxy-$\Delta^8$-octalin-2-ol (IV) as a viscous oil (5·03 g., 95%), $n_D^{15}$ 1·5173, $\nu_{max.}$ (in $CCl_4$) 3610 cm.$^{-1}$ (OH), no band in the carbonyl region.

The octalin-2-ol (1 g.) in pyridine (5 c.c.) was heated with acetic anhydride (0·4 c.c.) at 100° for 1 hr., then poured into 2N-hydrochloric acid (20 c.c.), and the product was isolated by ether. The resulting oil was poured in light petroleum through alumina (3 g.), followed by further light petroleum (50 c.c.). Evaporation gave an oil (0·9 g.) which was dissolved in light petroleum (*ca.* 10 c.c.) and kept overnight at −5°. 2-*Acetoxy*-1 : 1 : 10-*trimethyl-5-tetrahydropyranyloxy-*$\Delta^8$*-octalin* (0·2 g.) crystallised as prisms, m. p. 80—88° raised by further recrystallisation to 102·5—104·5° (Found: C, 71·3; H, 9·55. $C_{20}H_{32}O_4$ requires C, 71·4; H, 9·6%), $\nu_{max.}$ (in $CCl_4$) 1739 and 1238 (acetate) and 1075, 1062, and 1022 cm.$^{-1}$ (C·O·C·O·C). The residue (0·7 g.) from the mother-liquor of the crystals, m. p. 80—88°, showed the same infrared bands.

6-*Acetoxy*-5 : 5 : 9-*trimethyl*-$\Delta^{4(10)}$-*octalin*-1-*ol* (VI).—The acetate (V) (4·5 g. of oil) prepared from 1 : 1 : 10-trimethyl-5-tetrahydropyranyloxy-$\Delta^8$-octalin-2-ol (5 g.) was treated in methanol (45 c.c.) with hydrochloric acid (3 drops) at 40—45° for 20 min. Dilution with water and extraction with ether gave an oil (3·4 g.). Addition of light petroleum (b. p. 40—60°) to this oil led to 6-*acetoxy*-5 : 5 : 9-*trimethyl*-$\Delta^{4(10)}$-*octalin*-1-*ol* as prisms (1·85 g.), m. p. 97—98° (Found: C, 71·7; H, 9·85. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%), $\nu_{max.}$ (in $CS_2$) 3600 (OH), 1739 and 1238 (acetate), and 793 cm.$^{-1}$ (C:C).

6-*Acetoxy*-5 : 5 : 9-*trimethyl*-trans-*decalin*-1-*ol* (VII).—The octalinol (VI) (210 mg.) in acetic acid (15 c.c.) was hydrogenated in the presence of Adams platinum catalyst (100 mg.). Uptake of hydrogen ceased after 6 hr. Removal of the catalyst, evaporation under reduced pressure, and crystallisation at 0° from light petroleum gave the trans-*decalinol* as prisms, m. p. 93—95° (Found: C, 71·15; H, 10·25. $C_{15}H_{26}O_3$ requires C, 70·85; H, 10·3%). There was no infrared absorption band in $CS_2$ solution at 793 cm.$^{-1}$.

6-*Acetoxy*-5 : 5 : 9-*trimethyl*-trans-*decal*-1-*one* (VIII).—The decalinol (VII) (400 mg.) in acetone (25 c.c.) was treated with 8N-chromic acid (0·62 c.c.) by the method of Bowers *et al.*[12] After dilution with water, ethereal extraction afforded a solid (340 mg.) which crystallised from light petroleum (b. p. 40—60°) to give the *decalone* as needles, m. p. 92—96°, raised by sublimation at 75—80°/0·05 mm. to 96—97° (Found: C, 71·75; H, 9·5. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%), $\nu_{max.}$ (in $CS_2$) at 1710 (>CO), and 1739 and 1238 cm.$^{-1}$ (acetate).

1 : 1 : 10-*Trimethyl*-trans-*decalin*-2-*ol* (IX).—6-Acetoxy-5 : 5 : 9-trimethyl-*trans*-decal-1-one (740 mg.) in redistilled diethylene glycol (15 c.c.) was heated under reflux for 1 hr. with 100% hydrazine hydrate (1·45 c.c.) and potassium hydroxide (1·3 g.). The excess of water was then removed by distillation until the internal temperature reached 200°, then heating under reflux was continued for a further 4 hr. under nitrogen. After dilution with water, ethereal extraction afforded a solid (410 mg.) which on sublimation at 100—120°/14 mm. gave 1 : 1 : 10-*trimethyl*-trans-*decalin*-2-*ol* as plates, m. p. 60—65° (Found: C, 79·25; H, 12·45. $C_{13}H_{24}O$ requires C, 79·5; H, 12·3%), $\nu_{max.}$ (in $CCl_4$) 3636 (OH) and 1381 and 1364 cm.$^{-1}$ (*gem.*-dimethyl).

1 : 1 : 10-*Trimethyl*-trans-*decal*-2-*one* (X).—1 : 1 : 10-Trimethyl-*trans*-decalin-2-ol (200 mg.) in acetone (10 ml.) was treated with 8N-chromic acid (0·35 c.c.) as above.[12] After dilution with

[12] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548.

water, ethereal extraction afforded a liquid (194 mg.) which, distilled at 70—75°/0·3 mm., gave 1 : 1 : 10-*trimethyl*-trans-*decal*-2-*one*, $n_D^{17}$ 1·4950, m. p. 25—28° (Found: C, 80·4; H, 11·4. $C_{13}H_{22}O$ requires C, 80·35; H, 11·4%), $\nu_{max.}$ (liquid film) 1710 (>CO) and 1381 and 1365 cm.$^{-1}$ (*gem.*-dimethyl). The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 191—192°, from ethanol (Found: C, 60·85; H, 7·15; N, 14·9. $C_{19}H_{26}O_4N_4$ requires C, 60·95; H, 7·0; N, 14·95%). The *semicarbazone* formed needles, m. p. 218—219° (decomp. >210°), from ethanol (Found: C, 67·0; H, 9·95; N, 16·8. $C_{14}H_{25}ON_3$ requires C, 66·9; H, 10·05; N, 16·7%).

10-*Methyl*-$\Delta^{1(9)}$-*octal*-2-*one*.—2-Methyl*cyclo*hexanone (146 g.) was heated under reflux for 45 min. under nitrogen with potassium *tert.*-butoxide (from 39 g. of potassium) in *tert.*-butyl alcohol (1·2 l.). The solution was cooled to 20° during 1½ hr., then freshly distilled 1-diethylaminobutan-3-one (14·3 g.) was added with stirring during 45 min., the temperature rising to 60°. Stirring was continued for 16 hr. under nitrogen, then the solvent was removed. The residue was acidified to pH 2 with dilute sulphuric acid and extracted with ether, to give a mixture of 2-methyl*cyclo*hexanone and 10-methyl-$\Delta^{1(9)}$-octal-2-one. These were separated by distillation and 10-methyl-$\Delta^{1(9)}$-octal-2-one (56 g., 35%), b. p. 68°/0·1 mm., $n_D^{19}$ 1·5190, was obtained.

10-*Methyl*-trans-*decal*-2-*one* (XIII).—10-Methyl-$\Delta^{1(9)}$-octal-2-one (31 g.) in ether (150 c.c.) was added during 45 min. to a stirred solution of lithium (15 g.) in liquid ammonia (2 l.). After a further 45 min. ethanol was slowly added to discharge the blue colour and the ammonia allowed to evaporate. The residue was acidified to pH 1 and extracted with ether, to give 10-methyl-*trans*-decalin-2-ol (23 g.), b. p. 73—80°/0·1 mm., m. p. 72—74° [after crystallisation from light petroleum (b. p. 30—40°) and sublimation at 70°/0·05 mm.] (Found: C, 78·5; H, 12·0. Calc. for $C_{11}H_{20}O$: C, 78·5; H, 12·0%).

8N-Chromic acid was slowly added to a cooled solution of the decalinol (15·3 g.) in acetone (150 c.c.) until an orange colour persisted for 1—2 min. Most of the acetone was removed at 20°, the residue was treated with water, and the product isolated with ether. Distillation of the resultant oil gave 10-methyl-*trans*-decal-2-one (12·1 g.), b. p. 60°/0·1 mm., $n_D^{18\cdot5}$ 1·4918 (Found: C, 79·6; H, 10·9. Calc. for $C_{11}H_{18}O$: C, 79·5; H, 10·9%). The decalone was characterised as its 2 : 4-dinitrophenylhydrazone which crystallised as yellow plates, m. p. 178—180°, from ethyl acetate. Woodward *et al.*[10] give m. p. 177—178°.

3-*Hydroxymethylene*-10-*methyl*-trans-*decal*-2-*one*.—Sodium methoxide (from 1·86 g. of sodium) was dried at 160°/0·1 mm. for 1 hr., powdered, and suspended in dry benzene (25 c.c.) under nitrogen. Ethyl formate (11·1 g.) was slowly added to the stirred suspension, and 30 min. later the mixture was cooled in ice and treated during 1 hr. with 10-methyl-*trans*-decal-2-one (5 g.) in benzene (25 c.c.). More benzene (25 c.c.) was added and the mixture stirred at 20° under nitrogen for 18 hr. After dilution with benzene, the mixture was cooled in ice and cautiously acidified to pH 1. The organic layer was extracted with 2% potassium hydroxide solution. The aqueous alkaline solution was then washed with ether, cooled, and acidified as before, and the product isolated with ether and crystallised from light petroleum (b. p. 30—40°), to give 3-*hydroxymethylene*-10-*methyl*-trans-*decal*-2-*one* (5·6 g.), m. p. 73—74°, raised by sublimation at 70°/0·1 mm. to 75·5—76° (Found: C, 74·3; H, 9·4. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·35%), $\lambda_{max.}$ (in 50% ethanolic 0·05N-sodium hydroxide) 3150 Å (ε 18,750).

10-*Methyl*-2-*oxo*-trans-*decalin*-3-spiro-2′-(1′ : 3′-*dithian*) (XII).—3-Hydroxymethylene-10-methyl-*trans*-decal-2-one (4·03 g.), trimethylene ditoluene-*p*-thiosulphonate (9·35 g.), and potassium acetate (11·2 g.) in ethanol (150 c.c.) were heated under reflux for 7 hr. Evaporation of the solvent and dilution with water gave a solid, to which was added the material obtained on chloroform extraction of the aqueous layer. Crystallisation from ethanol gave the *spiran* (XII) (4·4 g.) as plates, m. p. 136·5—138° (partial sublimation) (Found: C, 62·5; H, 8·0. $C_{14}H_{22}OS_2$ requires C, 62·2; H, 8·2%), $\nu_{max.}$ (in $CS_2$) 1704 cm.$^{-1}$.

1 : 1 : 10-*Trimethyl*-2-*oxo*-trans-*decalin*-3-spiro-2′-(1′ : 3′-*dithian*) (XI).—Sodium (1·75 g.) was dissolved in vigorously stirred dry *tert.*-amyl alcohol (25 c.c.) under nitrogen by heating under reflux. When all solid material had dissolved the solution was concentrated to incipient crystallisation and the hot liquid rapidly transferred to a dish in a desiccator, which was slowly evacuated as the mass solidified. The resultant yellowish-white solid was powdered and dissolved in benzene (100 c.c.) under nitrogen. 10-Methyl-2-oxo-*trans*-decalin-3-*spiro*-2′-(1′ : 3′-dithian) (3·43 g.) in benzene (60 c.c.) was added with stirring. The solution was heated at 60° for 30 min., then cooled somewhat and treated with methyl iodide (18 g.) in benzene (25 c.c.). After 10 min. the temperature was raised and the solution heated under reflux for

5½ hr. under nitrogen, more methyl iodide (1 c.c. portions) being added at hourly intervals. Water (100 c.c.) was added and the organic phase separated and combined with a benzene extract of the neutralised aqueous phase. The benzene was removed and the residue in light petroleum–benzene solution filtered through deactivated alumina (15 g.). Evaporation gave a solid which crystallised from ethanol, to give 1 : 1 : 10-*trimethyl*-2-*oxo*-trans-*decalin*-3-spiro-2′-(1′ : 3′-*dithian*) as prisms (2·65 g.), m. p. 137—138° (with sublimation) (Found: C, 64·4; H, 9·95. $C_{16}H_{26}OS_2$ requires C, 64·4; H, 8·8%), $\nu_{max.}$ (in $CCl_4$) 1692 (>CO group) and 1382 and 1362 cm.$^{-1}$ (*gem.*-dimethyl).

1 : 1 : 10-*Trimethyl*-trans-*decal*-2-*one* (X).—The foregoing thioketal (635 mg.) and deactivated Raney nickel [7] (6·44 g. of settled suspension) were heated under reflux in ethanol (25 c.c.) for 6½ hr. and then kept overnight. Most of the supernatant liquid was decanted, the nickel was washed with hot ethanol, and the combined liquids were centrifuged. Evaporation under reduced pressure at low temperature gave an oil (400 mg.) which was distilled, to give 1 : 1 : 10-*trimethyl*-trans-*decal*-2-*one* (340 mg.), b. p. (bath) 60°/0·03 mm., $n_D^{17}$ 1·4954, m. p. 25—28° (Found: C, 80·7; H, 11·5. $C_{13}H_{22}O$ requires C, 80·4; H, 11·4%), $\nu_{max.}$ (liquid film) 1710 cm.$^{-1}$. The spectrum was identical with that of the 1 : 1 : 10-trimethyl-*trans*-decal-2-one prepared from 6-acetoxy-5 : 5 : 9-trimethyl-*trans*-decal-1-one.

The 2 : 4-dinitrophenylhydrazone formed orange needles (from ethanol–benzene [3 : 1]), m. p. 189—190° (decomp.), undepressed on admixture with the 2 : 4-dinitrophenylhydrazone of the 1 : 1 : 10-trimethyl-*trans*-decal-2-one prepared from 6-acetoxy-5 : 5 : 9-trimethyl-*trans*-decal-1-one. The semicarbazone formed needles (from ethanol), m. p. 218—219° (decomp.), undepressed on admixture with the authentic semicarbazone (similarly obtained).

1 : 1 : 10-*Trimethyl*-trans-*decalin*.—1 : 1 : 10-Trimethyl-*trans*-decal-2-one (520 mg.), 100% hydrazine hydrate (1·5 c.c.), potassium hydroxide (1·34 g.), and redistilled diethylene glycol (12 c.c.) were heated under reflux for 2 hr. under nitrogen. Water and excess of hydrazine were distilled until the internal temperature reached 210°, the distillate (2·5 c.c.) being retained. The mixture was then heated under reflux for 5 hr. under nitrogen. The distillate was then added back, together with water, and the product was isolated with ether as an oil which was percolated through alumina (5 g.) with light petroleum (25 c.c.). Distillation of the final oil afforded 1 : 1 : 10-*trimethyl*-trans-*decalin* (270 mg.), b. p. (bath-temp.) 105—110°/17 mm., $n_D^{17\cdot5}$ 1·4858 (Found: C, 85·9; H, 13·1. $C_{13}H_{24}$ requires C, 86·6; H, 13·4%), $\nu_{max.}$ (liquid film), no carbonyl band, bands at 1378 and 1365 cm.$^{-1}$ (*gem.*-dimethyl group).

*Wolff–Kishner Reduction of* 5 : 5 : 9-*Trimethyl*-trans-*decal*-1-*one*.[3]—5 : 5 : 9-Trimethyl-*trans*-decal-1-one (500 mg.) was reduced as described in the preceding experiment. The 1 : 1 : 10-trimethyldecalin (250 mg.) so obtained had b. p. (bath-temp.) 100—105°/10 mm., $n_D^{17}$ 1·4862. Its infrared absorption spectrum was identical with that of 1 : 1 : 10-trimethyl-*trans*-decalin obtained from 1 : 1 : 10-trimethyl-*trans*-decal-2-one.

The authors thank Professor E. R. H. Jones for his interest and Dr. F. Sondheimer for interesting discussion and for information before its publication. One of the authors (B. G.) thanks the Institute of Physics " Ruder Boskovic," Zagreb, Yugoslavia, and another (D. W.) the C.S.I.R.O., Australia, for maintenance grants.

The Dyson Perrins Laboratory, Oxford University. [*Received, September 9th*, 1957.]

## 123. *Mechanism and Stereochemistry of the Addition of Nitrogen Dioxide to Olefins.*

By J. C. D. Brand and I. D. R. Stevens.

The activity of bromotrichloromethane as a transfer agent in the reaction of nitrogen dioxide with *cyclo*hexene affords definite evidence of a free-radical mechanism.

The stereochemistry of addition of nitrogen dioxide radicals to *cyclo*hexene, 1-methyl*cyclo*hexene, and *cyclo*pentene has been determined by hydrolysis of the nitro-nitrite ester to nitro-alcohol, followed by hydrogenation under controlled conditions to the corresponding amino-alcohol of known configuration. On this basis 2-nitro*cyclo*hexyl nitrite (58% *trans*) and 2-nitro*cyclo*pentyl nitrite (84% *trans*) were produced with an excess of the *trans*-isomer; but the reaction with 1-methyl*cyclo*hexene was stereospecifically *trans*, yielding 1-methyl-*trans*-2-nitro*cyclo*hexyl nitrite. 2-Chloro*cyclo*hexyl nitrite (62% *trans*) and 2-nitro*cyclo*hexyl nitrite (62% *trans*) were formed non-stereospecifically in the reaction of nitryl chloride with *cyclo*hexene.

The reaction of dinitrogen tetroxide with simple olefins [1] was first placed on a firm experimental basis by Levy and his collaborators.[2] At that time interest in the chemistry of the nitronium ion ($NO_2^+$) stimulated the hypothesis,[2,3] consistent with the facts then known of the orientation of the addition, that the reaction involved heterolytic addition of the tetroxide as $NO_2^+NO_2^-$. The products (*vic.*-dinitro-compounds and nitro-nitrite esters) contain not less than one $C{-}NO_2$ group, as required by an explanation involving attack by $NO_2^+$.

Later evidence has eroded this argument considerably. Addition to diphenylacetylene (tolane) [4] and to hex-3-yne [5] is non-stereospecific; this result is not expected from a heterolytic process. The orientation of addition to methyl acrylate [6] is contrary to the Markovnikov rule. These results however are readily understood in terms of a free-radical mechanism: [6]

$$NO_2 + \rangle C{=}C \langle = \rangle C(NO_2)\cdot\dot{C} \langle \quad \ldots \quad (1)$$

$$\rangle C(NO_2)\cdot\dot{C} \langle + NO_2 = \rangle C(NO_2)\cdot C(NO_2) \langle \text{ and } \rangle C(NO_2)\cdot C(ONO) \langle \quad \ldots \quad (2)$$

Similar suggestions were advanced for the cognate reactions of nitric oxide,[7] dinitrogen trioxide,[8] and nitryl chloride [5,9] with simple olefins. We used transfer agents to detect free-radical intermediates in the reaction of *cyclo*hexene with nitrogen dioxide; the stereochemistry of the products of addition to *cyclo*hexene, 1-methyl*cyclo*hexene, and *cyclo*pentene was determined.

*Addition to* cyclo*Hexene in Presence of Bromotrichloromethane.*—Participation of transfer agents in the addition is suggested by the induced oxidation of the solvent when the reaction is carried out in a halogenocarbon medium,[2] and by the presence of a large proportion of bromine in the (unidentified) mixture of products from *cyclo*hexene and nitrogen dioxide in bromoform.[10] The reaction of *cyclo*hexene with nitrogen dioxide in mixed ether–bromotrichloromethane was studied in detail. Under " normal " conditions (no bromotrichloromethane) the products are 1 : 2-dinitro*cyclo*hexane and 2-nitro*cyclo*hexyl nitrite,[2] neither

[1] Riebsomer, *Chem. Rev.*, 1945, **36**, 157.
[2] Levy and Scaife, *J.*, 1946, 1093, 1100; Levy, Scaife, and Wilder-Smith, *J.*, 1946, 1096; 1948, 52, Baldock, Levy, and Scaife, *J.*, 1949, 2627.
[3] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, New York, 1953 p. 670.
[4] Campbell, Shavel, and Campbell, *J. Amer. Chem. Soc.*, 1953, **75**, 2400.
[5] Freeman and Emmons, *ibid.*, 1957, **79**, 1712.
[6] Schechter and Conrad, *ibid.*, 1953, **75**, 5610.
[7] Brown, *ibid.*, 1957, **79**, 2480.
[8] Schechter and Ley, *Chem. and Ind.*, 1955, 535.
[9] Schechter, Conrad, Daulton, and Kaplan, *J. Amer. Chem. Soc.*, 1952, **74**, 3052.
[10] Titov and Baryshnikova, *Doklady Akad. Nauk S.S.S.R.*, 1953, **91**, 1099.

XUM

of which was detected when the reaction was carried out in presence of the transfer agent (Table 1). As light was excluded, bromotrichloromethane can only have altered the character of the product in its capacity as a radical-transfer agent, and the total suppression of the " normal " products must mean that the heterolytic reaction, if it operates at all, is of very minor importance.

TABLE 1. *Products (moles %) of the reaction of* cyclo*hexene with bromotrichloromethane induced by nitrogen dioxide.*

| | | | | | |
|---|---|---|---|---|---|
| 1-Bromo-2-chloro*cyclo*hexane | 30·9 | 2-Chloro*cyclo*hexyl nitrate | 4·4 | Trichloronitromethane ... | 3·1 |
| 1-Bromo-2-nitro*cyclo*hexane | 28·7 | 1-Nitro*cyclo*hexene ..... | 3·6 | Nitrosyl chloride ..... | Small |
| 2-Chloro*cyclo*hexanol ..... | 27·7 | *cyclo*Hexene nitrosite ..... | 1·6 | | |

Apparently the primary reaction of bromotrichloromethane is with the 2-nitro*cyclo*hexyl radicals produced in step (1), forming 1-bromo-2-nitro*cyclo*hexane:

$$NO_2{\cdot}C_6H_{10}{\cdot} + BrCCl_3 = NO_2{\cdot}C_6H_{10}Br + {\cdot}CCl_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The remaining products are explained by reactions initiated by trichloromethyl radicals. Although the association of trichloromethyl with olefins is well known,[11] its reaction in the present system is with nitrogen dioxide, *viz.*,

$$ {\cdot}CCl_3 + NO_2 = CCl_3{\cdot}NO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

and

$$ {\cdot}CCl_3 + NO_2 = CCl_3O{\cdot} + NO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Trichloromethyl nitrite may be formed as a transient intermediate in step (5). It appears that the trichloromethoxy-radicals also decompose rapidly:

$$CCl_3O{\cdot} = Cl{\cdot} + Cl_2CO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

[Reaction (5) and (6) have been identified in the pyrolysis of trichloronitromethane.[12]] The chlorine atoms liberated are considered to initiate processes leading to the formation of 1-bromo-2-chloro*cyclo*hexane, 2-chloro*cyclo*hexanol, and 2-chloro*cyclo*hexyl nitrate (Table 1):

$$Cl{\cdot} + C_6H_{10} = ClC_6H_{10}{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$ClC_6H_{10}{\cdot} + BrCCl_3 = ClC_6H_{10}Br + {\cdot}CCl_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

$$ClC_6H_{10}{\cdot} + NO_2 = ClC_6H_{10}{\cdot}ONO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Step (8) represents the formation of 1-bromo-2-chloro*cyclo*hexane in a transfer step, analogous to (3), from a 2-chloro*cyclo*hexyl free radical. The origin of 2-chloro*cyclo*hexanol and 2-chloro*cyclo*hexyl nitrate is thought to be the reaction (9), the nitrite ester first produced being either oxidised to nitrate or hydrolysed during isolation. In principle the steps (5), (6), (7), and (8) are self-supporting, but the yield of 1-bromo-2-chloro*cyclo*hexane roughly equals the combined yield of 2-chloro*cyclo*hexanol and its nitrate ester, and thus on the average this cycle of reactions occurs only once before termination by (4) and (9).

*cyclo*Hexene nitrosite formation is related to the accumulation of nitric oxide [eqn. (5)] in the later stages of reaction,

$$NO_2{\cdot}C_6H_{10}{\cdot} + NO = NO_2{\cdot}C_6H_{10}{\cdot}NO \longrightarrow \text{Dimer}$$

(Nitric oxide itself does not attack a double bond at moderate temperature.[7,13]) Pyrolysis of *cyclo*hexene nitrosite during the distillation of the reaction product was probably the main source of 1-nitro*cyclo*hexene.

*Reaction of* cyclo*Hexene with Nitrogen Dioxide in Ether.*—Up to this point the evidence is wholly favourable to Schechter and Conrad's mechanism,[6] represented by eqn. (1) and

[11] Cadogan and Hey, *Quart. Rev.*, 1954, **8**, 308.
[12] Gray, *Trans. Faraday Soc.*, 1955, **51**, 1367.
[13] Rabinovitch and Looney, *J. Chem. Phys.*, 1955, **23**, 2439.

(2). However an alternative to step (2) that would be equally acceptable is (2*a*). Under certain conditions (2) and (2*a*) are kinetically distinguishable.

$$NO_2{\cdot}C_6H_{10}{\cdot} + N_2O_4 = NO_2{\cdot}C_6H_{10}{\cdot}NO_2 \text{ (or } NO_2{\cdot}C_6H_{10}{\cdot}ONO) + NO_2 \quad . \quad . \quad (2a)$$

Velocities of reaction were measured in ether solution at 5°: the degree of dissociation of dinitrogen tetroxide is then sufficiently small (<1%, by direct measurement) for the real and the virtual (stoicheiometric) dinitrogen tetroxide concentration to be equated. As the union of nitrogen dioxide radicals is extremely fast,[14] it can be shown that the apparent order of reaction with respect to $[N_2O_4]$ will be between 0·5 and 1 if (2) is appropriate rather than (2*a*), and between 0 and 1 if the rôles are reversed. The limits are controlled by the relative speeds of the reverse of reaction (1) and of (2) or (2*a*).

With $[N_2O_4] = 0{\cdot}03$—$0{\cdot}1$M the reaction was approximately of the first order in $[N_2O_4]$, $k = 0{\cdot}008_9$ l. moles$^{-1}$ sec.$^{-1}$ at 5°. (Similar kinetics apply to the reaction of nitrogen dioxide with ethylene and propene in the vapour phase at 160—260°, where the order with respect to *nitrogen dioxide* is 1·8.[15]) The fact that the reaction order with respect to tetroxide is near unity demonstrates that the reverse of reaction (1) is kinetically significant, in agreement with evidence that nitrogen dioxide catalyses the *cis–trans* isomerisation of olefins;[16] but it does not help to distinguish (2) from (2*a*), which would have been possible if the relative velocities had been such that the order was less than 0·5.

*Reaction of* cyclo*Hexene with Nitryl Chloride in Ether.*—Addition of nitrogen dioxide was also studied by letting nitryl chloride react with *cyclo*hexene. The composition of the product is summarised in Table 2, the experimental procedure being to allow hydrolysis of the nitrite esters to the corresponding hydroxy-compound to proceed before isolation. The formation of 1-chloro-2-nitro*cyclo*hexane, 1 : 2-dichloro*cyclo*hexane, and *cyclo*hexene nitrosite has been noted previously.[17] The reaction was conducted by distilling nitryl chloride in a current of oxygen into a solution of *cyclo*hexene in dry ether at 0°, the order of mixing of reagents being chosen to keep the concentration of nitryl chloride low and so to retard the reaction [18]

$$Cl{\cdot} + ClNO_2 = Cl_2 + NO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

which competes with *cyclo*hexene for the available chlorine atoms. However evidence presented later suggests that step (10) was important.

TABLE 2. *Products (moles %) of the reaction of nitryl chloride with* cyclo*hexene.*

| | | | |
|---|---|---|---|
| 1-Chloro-2-nitro*cyclo*hexane | 41·6 | 2-Nitro*cyclo*hexanol | 5·4 |
| *trans*-1 : 2-Dichloro*cyclo*hexane | 26·6 | *cyclo*Hexen-3-ol | 3·2 |
| 2-Chloro*cyclo*hexanol | 6·2 | *cyclo*Hexene nitrosite (?) | 7·6 |
| 2-Chloro*cyclo*hexyl nitrate | 6·4 | 1-Chloro-2-nitroso*cyclo*hexane (dimer) (?) | 2·8 |

The composition of the product supports the partial mechanism suggested by Schechter and his co-workers [9] that initiation occurs by step (1) and is succeeded by

$$NO_2{\cdot}C_6H_{10}{\cdot} + ClNO_2 = NO_2{\cdot}C_6H_{10}Cl + NO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

Because 2-nitro*cyclo*hexanol, but not 1 : 2-dinitro*cyclo*hexane, was identified in the product, it appears that the former is not produced by the step (2) but by an alternative path to (11), namely

$$NO_2{\cdot}C_6H_{10}{\cdot} + ClNO_2 = NO_2{\cdot}C_6H_{10}{\cdot}ONO + Cl{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

2-Chloro*cyclo*hexanol must be derived from the initial attack of a chlorine atom, for the

[14] Carrington and Davidson, *J. Phys. Chem.*, 1953, **57**, 418.
[15] Cottrell and Graham, *J.*, 1953, 556; 1954, 3644.
[16] Khan, *J. Chem. Phys.*, 1955, **23**, 2447.
[17] Price and Sears, *J. Amer. Chem. Soc.*, 1953, **75**, 3275.
[18] Volpe and Johnston, *ibid.*, 1956, **78**, 3903.

primary attack of nitrogen dioxide on an unsaturated system always establishes a C–N bond;[2,5,8] therefore the route to this product is the reaction (7) followed by

$$ClC_6H_{10}\cdot + ClNO_2 = ClC_6H_{10}\cdot ONO + Cl\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

In principle the steps (1) and (11), as well as (7) and (13), are self-supporting in this system, but the opportunities for cross-linking and termination are too numerous for a probable chain-length to be evaluated. The stereochemical configuration (Table 3) of 2-chloro- and 2-nitro-*cyclo*hexanol isolated from the reaction is discussed below.

The formation of 1 : 2-dichloro*cyclo*hexane requires careful evaluation. If it is produced homolytically, the mechanism would presumably involve the steps (7) and (14):

$$ClC_6H_{10}\cdot + NO_2Cl = C_6H_{10}Cl_2 + NO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

This is a possibility we cannot exclude. But the distinguishing feature of the reaction producing 1 : 2-dichloro*cyclo*hexane is that it is stereospecifically *trans* (see Experimental); therefore it appears more probable that the path to its formation is the reaction (10) followed by the normal, heterolytic addition of molecular chlorine. It is known that eqn. (10) represents a very fast step in the vapour-phase pyrolysis of nitryl chloride.[18]

The isolation of *cyclo*hex-2-enol suggests the abstraction of allylic hydrogen from *cyclo*hexene by a free radical. As this product is not formed from *cyclo*hexene and nitrogen dioxide we represent its formation by

$$C_6H_{10} + Cl\cdot = C_6H_9\cdot + HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

and

$$C_6H_9\cdot + NO_2 = C_6H_9\cdot ONO \longrightarrow C_6H_9\cdot OH$$

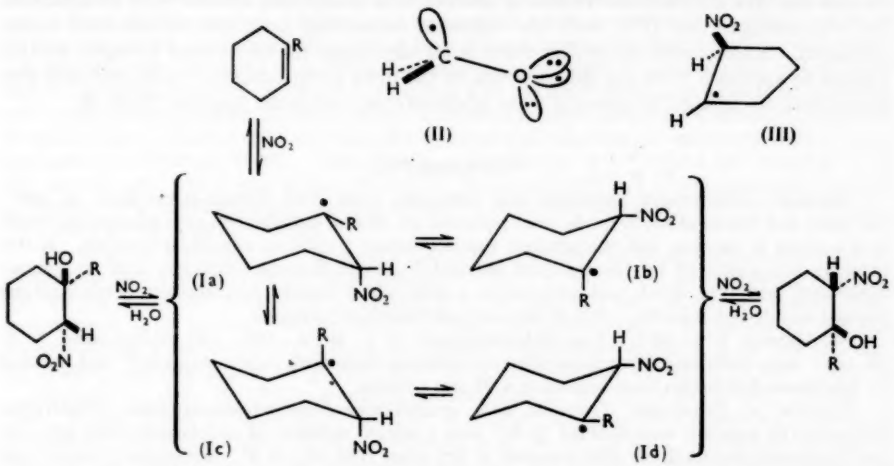
*Stereochemistry.*—The evidence relating to the stereochemistry of free-radical addition to double bonds is not extensive. Thermodynamic control operates in the photo-addition of bromotrichloromethane to *cis*- and *trans*-but-2-ene,[19a] in the copolymerisation of dichloroethylene with vinyl acetate,[20] and probably in the copolymerisation of but-2-ene with sulphur dioxide;[19b] in these reaction the lifetime of the intermediate radical apparently is sufficient for it to reach equilibrium among its conformations, and the composition of the product is the same from the *cis* and the *trans* isomer. On the other hand, addition of hydrogen bromide to *cis*- and *trans*-2-bromobut-2-ene is stereospecifically *trans* (the products are diastereoisomers of 2 : 3-dibromobutane[22d]) and that to 1-methyl-, 1-chloro-, and 1-bromo-*cyclo*hexene is almost quantitatively *trans*.[22a,b] Thiol-compounds and cyclic olefins give an excess of *trans*-addition, the proportion of *cis*-addition being kinetically controlled.[21,22c] The data relating to the reaction of cyclic olefins are summarised Table 3, above the results now obtained. Apart from the results for the thiol-compounds the most striking feature of the Table is the non-stereospecificity of addition to *cyclo*hexene compared with the stereospecifically *trans*-reaction of its 1-substituted derivatives, a distinction that applies also to the examples of addition to but-2-ene[19] and 2-bromobut-2-ene[22d] mentioned above. This aspect is not explained satisfactorily by any of the theories[19,21,22] advanced so far.

The problem is exemplified by the reaction of nitrogen dioxide with *cyclo*hexene and 1-methyl*cyclo*hexene (Table 3), where the presence of a methyl substituent is sufficient to swing the addition from non-stereospecificity to *trans*-stereospecificity. Our interpretation involves four postulates. (*a*) It is supposed that the radical intermediate in the reaction is pyramidal at the odd-electron centre. This postulate, also favoured by Bordwell and Hewett,[21] implies that there are four distinguishable conformations of the

[19] (*a*) Skell and Woodworth, *J. Amer. Chem. Soc.*, 1955, **77**, 4638; (*b*) Skell, Woodworth, and McNamara, *ibid.*, 1957, **79**, 1252.
[20] Mayo and Walling, *Chem. Rev.*, 1950, **46**, 191.
[21] Bordwell and Hewett, *J. Amer. Chem. Soc.*, 1957, **79**, 3493.
[22] (*a*) Goering, Abell, and Aycock, *ibid.*, 1952, **74**, 3588; (*b*) Goering and Sims, *ibid.*, 1955, **77**, 3465; (*c*) Goering, Relyea, and Larsen, *ibid.*, 1956, **78**, 348; (*d*) Goering and Larsen, *ibid.*, 1957, **79**, 2653.

intermediate, as in (Ia)—(Id); (*b*) that the particular conformation produced by the attack of the nitrogen dioxide radical on the olefin is that represented by (Ia); (*c*) that the speed of ring inversion, (Ia) ⇌ (Ib) or (Ic) ⇌ (Id), is slow compared with that of the second step for nitrogen dioxide addition. [This eliminates (Ib) and (Id) from consideration so far as the products are concerned.] Postulate (*d*) is a specific one mentioned later.

For the reaction of *cyclo*hexene with nitrogen dioxide, (*a*)—(*c*) permit the radical inversion (Ia) ⇌ (Ic) (R = H) to be rapid compared with both the ring inversions and the second step of the addition; thus the intermediate has the opportunity to distribute itself at equilibrium between (Ia) and (Ic). The non-stereospecific reaction is attributed to the simultaneous reactions of the two forms in the second step of the addition. The




inference that there is an element of thermodynamic control is in line with the evidence for thermodynamic control in additions to but-2-ene.[19]

TABLE 3. *Stereochemistry of radical addition to cyclic olefins.*

| Olefin | Adduct | Initiator | Product | *trans*-Addition (%) | Ref. |
|---|---|---|---|---|---|
| 1-Methyl*cyclo*hexene | HBr | Br | 1-Bromo-2-methyl*cyclo*hexane | ~100 | 22 [a] |
| 1-Methyl*cyclo*hexene | MeCOSH | MeCOS | 2-Methyl*cyclo*hexyl thiolacetate | 85 | 21 |
| 1-Bromo*cyclo*hexene | HBr | Br | 1 : 2-Dibromo*cyclo*hexane | 99·5 | 22 [b] |
| 1-Chloro*cyclo*hexene | HBr | Br | 1-Bromo-2-chloro*cyclo*hexane | 99·7 | 22 [b] |
| 1-Chloro*cyclo*hexene | $H_2S$ | HS | 2-Chloro*cyclo*hexanethiol | 86—93 | 22 [c] |
| 1-Methyl*cyclo*pentene | MeCOSH | MeCOS | 2-Methyl*cyclo*pentyl thiolacetate | 70 | 21 |
| *cyclo*Hexene | $N_2O_4$ | $NO_2$ | 2-Nitro*cyclo*hexanol | 58 | This paper |
| *cyclo*Hexene ..... | $NO_2Cl$ | $NO_2$ | 2-Nitro*cyclo*hexanol | 62 | ,, |
| *cyclo*Hexene | $NO_2Cl$ | Cl | 2-Chloro*cyclo*hexanol | 62 | ,, |
| 1-Methyl*cyclo*hexene | $N_2O_4$ | $NO_2$ | 1-Methyl-2-nitro*cyclo*hexanol | ~100 | ,, |
| *cyclo*Pentene | $N_2O_4$ | $NO_2$ | 2-Nitro*cyclo*pentanol | 84 | ,, |

The fourth postulate (*d*) is that, when R = Me, steric factors (especially the **1 : 3** repulsions) raise the energy of (Ic) considerably above that of (Ia), so that the lifetime of (Ic) is short in comparison with that of (Ia). {Possibly the potential energy rises continuously as the methyl group is displaced from the equatorial position [as in (Ia)] to the axial position (Ic), the steric repulsion being sufficient to eliminate the potential minimum in the conformation (Ic).} Consequently the reaction of methyl*cyclo*hexene will be associated with a very large excess of *trans* addition, that is, with a stereospecific reaction arising from kinetic control.

The assumption of a pyramidal radical needs careful qualification. Methyl radicals are planar, or nearly so.[23] However the diradical, excited electronic state of formaldehyde is pyramidal with the ethane-like configuration (II),[24] and examples are known of radical centres at the bridgehead of bicyclic compounds where the configuration must be pyramidal.[25] Our interpretation of this evidence is that an odd electron has no strong stereochemical preference; and that *a pyramidal configuration may be expected when the alternative planar configuration eclipses two bonds* or a bond and a non-bonding electron. Applied to *six-membered* ring radicals and to simple acyclic radicals from ethyl upwards, this hypothesis predicts a pyramidal configuration. For *five-membered* ring radicals there is no clear advantage in the pyramidal arrangement and the configuration may be planar. In this case the intermediate radical in the reaction of nitrogen dioxide with *cyclo*pentene has the configuration (III) with the valencies emanating from the odd-electron centre coplanar. Scale models show that there is an advantage for the second nitrogen dioxide radical to approach from the side opposite to the nitro-group already established, and this is sufficient to explain the excess of *trans* addition observed in the reaction (Table 3).

## Experimental

*Materials.*—Dinitrogen tetroxide was prepared from lead nitrate–silver-sand at 500°: moisture and traces of nitric oxide were removed by several distillations over phosphoric oxide in a current of oxygen, and the product was condensed (−80°) as colourless crystals. Nitryl chloride was prepared by the standard method,[26] passed through sulphuric acid to remove dinitrogen tetroxide, dried, and collected as a pale yellow liquid: spectrophotometric analysis showed no nitrosyl chloride, <3% of chlorine, and traces of tetroxide.

*cyclo*Hexene, b. p. 83·5°, 1-methyl*cyclo*hexene, b. p. 107·4—108°, and *cyclo*pentene, b. p. 43—44°, were freed from hydroperoxides by refluxing them with cupric stearate [27] and purified by fractional distillation from sodium in a 25 cm. column.

*Reaction of Dinitrogen Tetroxide with* cyclo*Hexene–Bromotrichloromethane.*—Dinitrogen tetroxide (98 mmoles) was distilled (3 hr.) into a stirred solution of *cyclo*hexene (294 mmoles) and bromotrichloromethane (980 mmoles) in dry ether (150 ml.) at 0°. Preliminary separation in a film evaporator yielded an oil (i) and a volatile fraction (ii) composed mainly of ether and bromotrichloromethane. The oil (i) was washed with water, and the aqueous washings buffered to pH 5—6 with sodium hydrogen carbonate and extracted continuously with ether: fractionation of material from the ether extract yielded 2-chloro*cyclo*hexanol (14·1 mmoles), b. p. 79—80°/18 mm., and a less volatile fraction (0·3 g.) from which a little *trans-cyclo*hexane-1 : 2-diol, m. p. and mixed m. p. 99°, was isolated. The portion of (i) insoluble in water was dried azeotropically with benzene and separated by distillation in a 4″ Vigreux column into fractions (iii), b. p. 47—89°/0·7 mm. (the bulk boiled at 47—49°), and (iv), b. p. 94—108°/1·5 mm. The distillation was interrupted at intervals to extract *cyclo*hexene nitrosite, m. p. 153° (decomp.) (lit.,[2] m. p. 152°, decomp.) after crystallisation from ethyl acetate, which otherwise pyrolysed in the column to 1-nitro*cyclo*hexene and oxides of nitrogen. A portion of (iii) dissolved in light petroleum (b. p. 40—60°) and chromatographed over activated silica yielded 1-bromo-2-chloro*cyclo*hexane, b. p. 44°/0·6 mm., $n_D^{20}$ 1·5167 (the *cis* and the *trans* isomer have $n_D^{25}$ 1·5238 and 1·5173, respectively [22b]) (Found: C, 36·2; H, 5·21. Calc. for $C_6H_{10}BrCl$: C, 36·5; H, 5·10%): the second principal component of (iii) was 2-chloro*cyclo*hexanol, and the fraction was eventually combined with (v). Fraction (iv) was treated with 85% phosphoric acid, washed dried with benzene, and redistilled to yield a pale yellow oil from which 1-*bromo*-2-*nitro*cyclo*hexane* (20·7 mmoles), m. p. 38·5—39° from light petroleum, $\lambda_{max.}$ 2780 (log $\varepsilon_{max.}$ 1·36), $\lambda_{min.}$ 2550 Å (1·22) in ethanol (Found: C, 35·0; H, 4·94; N, 6·60; Br, 38·2. $C_6H_{10}O_2NBr$ requires C, 34·6; H, 4·84; N, 6·73; Br, 38·4%), crystallised on standing. The content of the non-crystalline portion of (iv) was determined by infrared analysis: 1-bromo-2-nitro*cyclo*hexane (34·2 mmoles), 2-chloro*cyclo*hexyl nitrate (8·5 mmoles), 1-nitro*cyclo*hexene (6·8 mmoles), and 1-bromo-2-chloro*cyclo*hexane (2·5 mmoles):

[23] Herzberg and Shoosmith, *Canad. J. Phys.*, 1956, **34**, 523.
[24] Brand, *J.*, 1956, 858.
[25] Kharasch, Englemann, and Urry, *J. Amer. Chem. Soc.*, 1943, **65**, 2428.
[26] Schechter and Kaplan, "Inorganic Syntheses," McGraw-Hill, London, 1952, Vol. IV, p. 52.
[27] George and Robertson, *Trans. Faraday Soc.*, 1946, **42**, 217.

this result checked satisfactorily with a Carius estimation of total halogen (83·5% of mixed silver halide. Calc. 84·6%).

Distillation of the volatile fraction (ii) yielded *cyclo*hexene (*ca.* 10 mmoles), bromotrichloromethane (460 mmoles), and a residual oil (v), b. p. 40—45°/0·8 mm., of 2-chloro*cyclo*hexanol and 1-bromo-2-chloro*cyclo*hexane. (iii) and (v) were united and the composition, measured by infrared analysis, was 2-chloro*cyclo*hexanol, 38·9 mmoles, and 1-bromo-2-chloro*cyclo*hexane, 56·5 mmoles. The recovered bromotrichloromethane fraction contained trichloronitromethane (~6 mmoles) and some nitrosyl chloride (1770 cm.$^{-1}$ band). The overall yield, based on dinitrogen tetroxide, was 69%.

*Reaction of Nitryl Chloride with* cyclo*Hexene*.—Nitryl chloride (295 mmoles) was distilled slowly in a current of oxygen into a stirred solution of *cyclo*hexene (324 mmoles) in dry ether (200 ml.) at 0°. Moisture was excluded. The solution became deep blue during the reaction and a white solid separated. Solvent was removed in a film evaporator and solid product (i) (3·96 g.) filtered off: the liquid product was dissolved in pentane and washed repeatedly with water. The residual water-insoluble oil (ii) from the pentane layer was dried azeotropically with benzene and the infrared spectrum recorded: comparison with reference spectra established the presence of 1-chloro-2-nitro*cyclo*hexane (102 mmoles), 2-chloro*cyclo*hexyl nitrate (15·6 mmoles), and *trans*-1 : 2-dichloro*cyclo*hexane (65·2 mmoles), the infrared analyses being in agreement with a Carius estimation of chlorine (27·2%. Calc. 27·5%). Distillation of (ii) gave a first fraction, b. p. 78—85°/15 mm., which was washed with 85% phosphoric acid and chromatographed in light petroleum over activated silica, yielding *trans*-1 : 2-dichloro*cyclo*hexane, b. p. 70—71°/12 mm., $n_D^{19}$ 1·4904 (lit. $n_D^{20}$ 1·4904,[28] 1·4910 [29]).

The aqueous washings (1·2 l.) were extracted with ether and the oil so obtained separated by distillation in a 4 in. column into three fractions: (iii) b. p. 68—76°/12 mm. (2·86 g.), (iv) b. p. 76—80°/12 mm. (0·45 g.), and (v) a mixture, b. p. 78—84°/0·25 mm., of *cis*- and *trans*-2-nitro-*cyclo*hexanol (11·7 mmoles) distinguished by their infrared spectra. A portion of (iii) was fractionated in a small column (12 theoretical plates) into *cyclo*hexen-3-ol [b. p. 64—66°/11 mm., $n_D^{16}$ 1·4858; phenylurethane, m. p. 106° (lit.,[30] m. p. 107°) (Found: C, 72·1; H, 7·2. Calc. for $C_{13}H_{15}O_2N$: C, 71·9; H, 7·0%); α-naphthylurethane, m. p. 155° (lit.,[30] m. p. 155°) (Found: C, 76·6; H, 6·0. Calc. for $C_{17}H_{17}O_2N$: C, 76·4; H, 6·4%)] and a mixture (identified by infrared absorption) of *cis*- and *trans*-2-chloro*cyclo*hexanol, b. p. 70—71°/11 mm. According to infrared analysis the composition of (iii) was *cyclo*hexen-3-ol, 7·9 mmoles; 2-chloro*cyclo*hexanol (by difference), 13·5 mmoles, in fair agreement with a Carius estimation (Cl, 19·7. Calc. 18·5%). The small fraction (iv) contained *cis* and *trans* isomers of 2-chloro*cyclo*hexanol (1·7 mmoles) and 2-nitro*cyclo*hexanol (1·6 mmoles).

The solid (i) was not positively identified. It was apparently a mixture of dimeric 1-chloro-2-nitroso*cyclo*hexane and 1-nitro-2-nitroso*cyclo*hexane (*cyclo*hexene nitrosite) and was analysed on this basis by Carius estimation (Cl, 6·1%). The overall yield was 83%, based on nitryl chloride.

*Addition of Dinitrogen Tetroxide to* cyclo*Hexene*, 1-*Methyl*cyclo*hexene, and* cyclo*Pentene*.—Dinitrogen tetroxide was distilled slowly in oxygen into a stirred solution of the olefin (1·1 equiv.) in dry ether at 0°. In experiments with *cyclo*hexene the method of isolation was that of Baldock, Levy, and Scaife.[2] With 1-methyl*cyclo*hexene and *cyclo*pentene it was an advantage to collect the involatile oil from a film evaporator in methanol at −80°; on warming to 0° the nitro-nitrite was converted into nitro-alcohol and methyl nitrite by trans-esterification, urea being added to destroy small amounts of nitrous acid liberated by hydrolysis. Concentration *in vacuo* yielded a mixture of dinitro-compound, nitro-alcohol, and nitro-nitrate ester, which was dissolved in benzene–light petroleum and extracted repeatedly with water: nitro-alcohol (and some nitro-nitrate) were recovered from the aqueous washings by extraction with chloroform. The purification and later treatment of the crude nitro-alcohol is described below.

A portion of the residual oil from the reaction with *cyclo*hexene was dried with benzene and chromatographed in benzene over activated silica. The product, an oil, crystallised on standing, yielding 1 : 2-dinitro*cyclo*hexane, m. p. 46° after crystallisation from chloroform–light petroleum (Found: C, 41·7; H, 5·5; N, 16·3. Calc. for $C_6H_{10}O_4N_2$: C, 41·4; H, 5·8; N, 16·1%). (Baldock, Levy, and Scaife [2] isolated this compound as an oil, b. p. 110—114°/<1 mm.). By analogy with the corresponding nitro-alcohol the crystals were probably the *trans*-isomer, but

[28] Stevens and Grummitt, *J. Amer. Chem. Soc.*, 1952, **74**, 4876.
[29] Bohme and Schmitz, *Chem. Ber.*, 1955, **88**, 357.
[30] Clarke and Owen, *J.*, 1950, 2103.

the compound resisted hydrogenation under stereochemically unambiguous conditions and the configuration was not determined. The water-insoluble oil from the reaction with 1-methyl*cyclo*hexene crystallised after distillation, b. p. 110°/0·2 mm., yielding 1-*methyl*-trans-1 : 2-*dinitro*cyclo*hexane*, m. p. 90·5° after sublimation *in vacuo* or crystallisation from *cyclo*hexane (Found: C, 44·8; H, 6·1; N, 14·7. $C_7H_{12}O_4N_2$ requires C, 44·7; H, 6·4; N, 14·9%). The *trans* configuration was assigned on the basis of the stereospecifically *trans* character of the reaction producing the corresponding nitro-alcohol.

*Stereochemical Configuration.*—Nitrite ester hydrolysis occurs by O–N bond fission in all known cases,[31] and is assumed not to influence configuration. The configuration of the nitro-alcohols was determined by hydrogenation to the corresponding amino-alcohol of known or determinable configuration. Adams's catalyst equilibrates the stereoisomers of the nitro-alcohol and could not be used; but palladised charcoal was satisfactory.

2-*Nitro*cyclo*hexanol.*—Fractionation of the mixture of nitro-alcohols yielded a first fraction, b. p. 82·5°/1·3 mm., ν(C–OH) 974 cm.$^{-1}$ in chloroform, of *cis*-, and a final fraction, b. p. 88°/1·7 mm., of *trans*-2-nitro*cyclo*hexanol, ν(C–OH) 1074 cm.$^{-1}$, m. p. 46·5—47° (lit.,[2] m. p. 47—48°) after crystallisation from chloroform, $\lambda_{max.}$ 2790 (log $\varepsilon_{max.}$ 1·54), $\lambda_{min.}$ 2550 Å (1·29) in ethanol. The configuration of the *trans*-isomer was established by hydrogenation (Pd–charcoal) (85% yield) and benzoylation of the amino-alcohol (method of Leffler and Adams[32]; 93% yield), yielding *trans*-2-benzamido*cyclo*hexanol, m. p. and mixed m. p. 169° (lit.,[33] m. p. 171° corr.). Treated similarly, *cis*-2-nitro*cyclo*hexanol yielded *cis*-2-amino*cyclo*hexanol hydrochloride, m. p. 184° (lit.,[33] m. p. 185—187° corr.), and *cis*-2-benzamido*cyclo*hexanol, m. p. and mixed m. p. 183° (lit.,[33] m. p. 183—185° corr.).

The composition of the 2-nitro*cyclo*hexanol isolated from the reaction was determined by thermal analysis of the mixture of *cis*- and *trans*-2-benzamido*cyclo*hexanol produced by hydrogenation (Pd–charcoal) and benzoylation: *trans*, 58%; *cis*, 42%. The proportion of isomers resembled closely that of the equilibrium mixture of nitro-alcohols prepared by the neutralisation of a solution of 2-nitro*cyclo*hexanol in 5% sodium hydroxide with a 20% aqueous solution of urea acetate: to test whether equilibration had occurred during isolation from the preparation, *trans*-2-nitro*cyclo*hexanol, m. p. 46°, was dissolved in aqueous acid (0·1M), allowed to stand (2 hr. at 20°), and recovered after neutralisation by continuous extraction with ether. (These conditions were more extreme than in the actual isolation of crude nitro*cyclo*hexanol.) The product (91% recovery) had m. p. 43—46°, showing that epimerisation had not occurred under acid conditions.

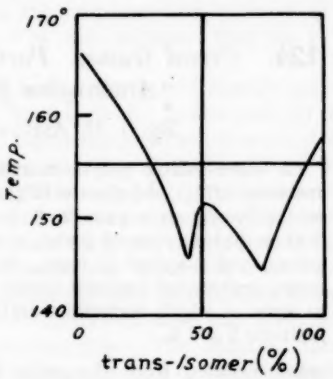
1-*Methyl*-2-*nitro*cyclo*hexanol.*—The water-soluble product from the reaction of 1-methyl*cyclo*hexene crystallised on standing and was purified by sublimation *in vacuo* (85% recovery), yielding 1-*methyl*-trans-2-*nitro*cyclo*hexanol*, m. p. 72°, $\lambda_{max.}$ 2820 (log $\varepsilon_{max.}$ 1·82), $\lambda_{min.}$ 2560 Å (1·56) in ethanol, ν(C–OH) 992 or 928 cm.$^{-1}$ in chloroform (Found: C, 52·8; H, 7·9; N, 8·9. $C_7H_{13}O_3N$ requires C, 52·8; H, 8·2; N, 8·8%). The stereochemistry was established by hydrogenation (Pd–charcoal) to *trans*-2-amino-1-methyl*cyclo*hexanol (hydrochloride, m. p. 161·5°, undepressed by admixture with an authentic sample obtained by ammonolysis of 1 : 2-epoxy-1-methyl*cyclo*hexane. Mousseron and Granger[34] record m. p. 148—149°) which yielded on benzoylation[32] trans-2-*benzamido*-1-*methyl*cyclo*hexanol*, m. p. and mixed m. p. 180° (Found: C, 72·2; H, 8·2. $C_{14}H_{19}O_3N$ requires C, 72·1; H, 8·2%). A careful examination of the residues gave no evidence of products derived from the *cis*-nitro-alcohol.

The following experiments showed that there was no appreciable amount of *cis* $\rightleftharpoons$ *trans* interconversion of the isomers of the nitro-alcohol during isolation. (*a*) 1-Methyl-*trans*-2-nitro*cyclo*hexanol was dissolved in deuterium oxide containing DCl ($2 \times 10^{-4}$M) and allowed to stand: no infrared absorption due to a C–D group was detected in the recovered material. (This covers the possibility of epimerisation of the nitro-alcohol in the aqueous phase during its extraction with water from the total mixture of products.) (*b*) The *trans*-nitro-alcohol was dissolved in methanolic hydrogen chloride (~$10^{2}$M) enriched with deuterium (2·25 atoms % of D), and allowed to stand (18 hr. at 20°). (The conditions here were considerably more exacting than in the actual isolation, where the methanolic solution from the film evaporator was kept for *ca.* 2 hr. only at 0°.) The recovered nitro-alcohol, analysed by

[31] Allen, *J.*, 1954, 1968.
[32] Leffler and Adams, *J. Amer. Chem. Soc.*, 1937, **59**, 2255.
[33] Johnson and Schubert, *ibid.*, 1950, **72**, 2187.
[34] Mousseron and Granger, *Bull. Soc. chim. France*, 1947, 843.

determination of the deuterium content of the combustion water (we are indebted for this measurement to Miss A. W. P. Jarvie), contained 0·244 ± 0·005 atom % of D, corresponding to the exchange of 1·29 atoms of hydrogen. Therefore about 30% of the hydrogen of the $>CH{\cdot}NO_2$ group had exchanged under these conditions (exchange within the OH group accounts for 1·0 atom). The rate of exchange sets an upper limit to the rate of epimerisation of the nitro-alcohol; and as the exposure in the preparation was considerably less severe than under the test conditions for exchange we conclude, with a margin of safety, that epimerisation was not significant.

2-*Nitro*cyclo*pentanol*.—The water-soluble product from the reaction with *cyclo*pentene was dissolved in benzene and washed with aqueous sodium hydrogen carbonate to remove a carboxylic acid impurity, and the residual oil distilled. (Only 77% of the material distilled smoothly, even when the distillation was interrupted and the contents of the flask were extracted with chloroform; the remainder suffered a low-order explosion.) The distillate was a mixture of *cis*- and *trans*-2-nitro*cyclo*pentanol, b. p. 78—79°/0·25 mm., and was converted by hydrogenation




*Freezing-point diagram for* cis- *and* trans-2-*p*-*nitrobenzamidocyclopentanol, illustrating the formation of a* 1 : 1-*complex.*

(Pd–charcoal) and *p*-nitrobenzoylation [33] into the corresponding mixture of *cis*- and *trans*-2-*p*-nitrobenzamido*cyclo*pentanol (78% yield), from which the *trans* isomer, m. p. 157·5° (lit.,[35] m. p. 160° corr.), was isolated by crystallisation from aqueous ethanol. Confirmation was obtained by treatment with thionyl chloride,[35] yielding *cis*-2-*p*-nitrobenzamido*cyclo*pentanol, m. p. 165—166° (lit.,[35] m. p. 167° corr.). Finally, the composition of the mixture was established by thermal analysis of the mixed *cis*- and *trans*-2-*p*-nitrobenzamido*cyclo*pentanol: *trans*, 84%; *cis*, 16% (Figure).

Retention of the stereochemical integrity of the epimeric nitro-alcohols was assumed by analogy with the two previous cases.

*Infrared Analyses*.—The isomeric composition of the samples of 2-chloro*cyclo*hexanol and 2-nitro*cyclo*hexanol isolated from the reaction of *cyclo*hexene with nitryl chloride was determined by infrared analysis (in carbon disulphide) by use of bands identified in the reference spectra of the pure isomers as characteristic of the stereochemical configuration. Independent analyses for the isomers of 2-chloro*cyclo*hexanol were in good agreement.

| Band (cm.$^{-1}$) | 2-Chloro*cyclo*hexanol *cis* (%) | *trans* (%) | Band (cm.$^{-1}$) | 2-Nitro*cyclo*hexanol *cis* (%) | *trans* (%) |
|---|---|---|---|---|---|
| 796 | — | 62·$_3$ | 862 | — | 62·$_3$ |
| 809 | 38·$_6$ | — | | | |

The specimen of 1 : 2-dichloro*cyclo*hexane isolated from the reaction with nitryl chloride showed no absorption due to the *cis* isomer (0·5 mm. liquid film).

When it was desired to estimate *cis* and *trans* isomers together the band chosen was common to both and had, so far as possible, the same intensity in the reference spectra of the individual isomers.

*Velocity Measurements*.—The velocity of reaction of nitrogen dioxide with *cyclo*hexene was

[35] McCasland and Smith, *J. Amer. Chem. Soc.*, 1950, **72**, 2190.

determined in ether solution at 5° from the change of optical density at 4358 Å. At this wavelength light was absorbed by nitrogen dioxide but not by dinitrogen tetroxide.[36] With *cyclo*hexene in excess, the individual runs were of first order. To allow for the small degree of dissociation of dinitrogen tetroxide in these conditions, the slope of a plot of log (optical density) against time was identified with $k/(2 \times 2{\cdot}3)$, where $k$ (sec.$^{-1}$) was the apparent first-order rate constant.

Reference infrared spectra and microanalyses were by Dr. G. Eglinton, Mr. J. M. L. Cameron, and their colleagues. A Carnegie Senior Scholarship (to I. D. R. S.) is gratefully acknowledged. We thank Miss A. W. P. Jarvie for the experiment indicated, and Professor D. H. R. Barton, F.R.S., for his interest.

THE UNIVERSITY, GLASGOW, W.2. [*Received, September 18th*, 1957.]

[36] Hall and Blacet, *J. Chem. Phys.*, 1952, **20**, 1745.

---

## 124. *Cereal Gums. Part III.* The Constitution of an Araboxylan from Barley Flour.*

By G. O. ASPINALL and R. J. FERRIER.

A water-soluble polysaccharide from barley flour gave xylose (59%), arabinose (37%), and glucose (4%) on hydrolysis. Hydrolysis of the methylated polysaccharide gave 2 : 3 : 5-tri-*O*-methyl-L-arabinose (3 parts), 2 : 3-di-*O*-methyl-D-xylose (3 parts), a mixture (1 part) of 2- and 3-*O*-methyl-D-xylose, and D-xylose (1 part). It is concluded that the highly branched barley araboxylan contains chains of 1 : 4-linked β-D-xylopyranose residues to some of which terminal L-arabofuranose residues are attached through positions 2 and 3.

BARLEY gum, isolated from the grain by aqueous extraction, is a mixture of polysaccharides containing residues of glucose, xylose, and arabinose.[1] Preece and Mackenzie [1] isolated the major component, a β-glucan, by fractional precipitation from aqueous solution by addition of ammonium sulphate. It was shown in Part I [2] that this polysaccharide contains unbranched chains of β-D-glucopyranose residues with approximately equal proportions of 1 : 3- and 1 : 4-linkages. Other fractions from barley gum gave mainly xylose and arabinose on hydrolysis, but a pure pentosan was not obtained by this method. An indication that the barley pentosan is similar to that found in wheat flour [3] was obtained by Gilles, Meredith, and Smith [4] who isolated three components on fractionation of methylated barley gum: (*a*) a methylated araboxylan; (*b*) a methylated α-glucan; and (*c*) a methylated β-glucan. Hydrolysis of the methylated araboxylan gave 2 : 3 : 5-tri-*O*-methylarabinose (1 part), 2 : 3-di-*O*-methylxylose (12 parts), 2-*O*-methylxylose (4 parts), and xylose (2 parts). As part of a series of structural investigations of the polysaccharide components of barley,[2,5,6] we now report a more detailed study of the barley-flour araboxylan.

Barley gum, isolated from the flour by aqueous extraction at 40°,[1] was fractionated by addition of ammonium sulphate to the aqueous solution. Fractions rich in pentosan, but still containing appreciable quantities of β-glucan, were precipitated at high concentrations of ammonium sulphate. Acetylation of the mixture of polysaccharides, followed by fractional precipitation of the acetates from acetone solution by the addition of light

* Part II, *J.*, 1957, 4469.

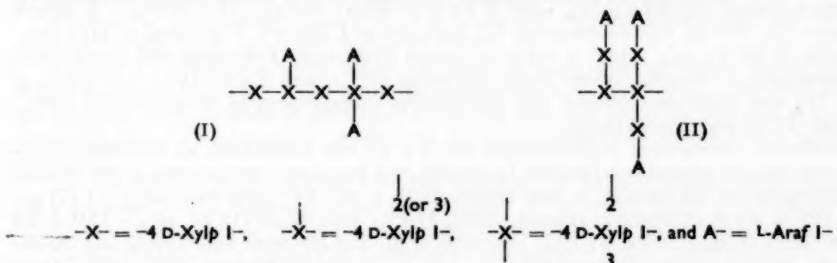
[1] Preece and Mackenzie, *J. Inst. Brewing*, 1952, **58**, 353, 457.
[2] Perlin, *Cereal Chem.*, 1951, **28**, 370, 382.
[3] Montgomery and Smith, *J. Amer. Chem. Soc.*, 1955, **77**, 2834, 3325.
[4] Aspinall and Telfer, *J.*, 1954, 3519.
[5] McWilliam and Percival, *J.*, 1951, 2259; Aspinall, Hirst, and McArthur, *J.*, 1955, 3075.
[6] Aspinall and Ferrier, *J.*, 1957, 4188.

XUM

petroleum, afforded substantially pure acetylated araboxylan. Hydrolysis of a sample of pentosan, regenerated from the acetate, gave xylose (59%), arabinose (37%), and glucose (4%).

The acetylated araboxylan was simultaneously deacetylated and methylated. Hydrolysis of a sample of the methylated polysaccharide and quantitative paper chromatography of the hydrolysate [7] showed the presence of tri-*O*-methyl- (41%), di-*O*-methyl- (36%), mono-*O*-methyl- (10%), and unsubstituted (13%) pentose. The mixture of methylated sugars obtained on hydrolysis of the methylated polysaccharide was fractionated on cellulose to give 2 : 3 : 5-tri-*O*-methyl-L-arabinose (39%), 2 : 3-di-*O*-methyl-D-xylose (36%), and D-xylose (14%), characterised as crystalline derivatives, and a mixture of mono-*O*-methylxyloses (11%). Paper ionophoresis showed that the mono-*O*-methylxylose fraction contained both the 2- and the 3-methyl ether, and the optical rotation of the syrupy mixture of sugars showed these to be present in the approximate ratio of 2 : 1. A portion of the mixture was converted into the corresponding mixture of methyl pyranosides, and the consumption of periodate, 0·76 mol., indicated that the 2- and the 3-methyl ether were present in the ratio of 3 : 1.

Several possible structures for the repeating unit of the polysaccharide may be put forward on the basis of these results, (I) and (II) being typical. In structure (I) the backbone of D-xylopyranose residues is linear and the L-arabofuranose residues are attached as single unit side-chains. In structure (II), on the other hand, the backbone of xylose residues is branched and the longer side-chains are terminated by arabofuranose residues. The following results provide evidence in favour of structure (I). The methylated araboxylan was heated with dilute aqueous methanolic hydrogen chloride under controlled conditions. The degraded methylated polysaccharide was separated from methylated sugars formed during the mild hydrolysis, and chromatographic examination of the sugars showed that about a quarter of the 2 : 3 : 5-tri-*O*-methylarabinose had been selectively removed, together with only a trace of di-*O*-methylxylose. The degraded methylated polysaccharide was remethylated and hydrolysed; quantitative estimation showed that 2 : 3 : 5-tri-*O*-methylarabinose and 2 : 3 : 4-tri-*O*-methylxylose were present in the hydrolysate in the ratio of 11 : 1. For an araboxylan of structure (I) mild hydrolysis of the methylated polysaccharide followed by remethylation would cause no significant increase in xylose end-groups. On the other hand, with an araboxylan of structure (II), these operations would yield a methylated degraded polysaccharide with an increased number of xylose end-groups, each terminal arabinose removed giving rise to a terminal xylose residue. Thus, removal of approximately one quarter of the arabinose residues




followed by remethylation would result in the formation of methylated degraded araboxylan containing arabinose and xylose end-groups in the proportion of 3 : 1. It follows from the observed ratio of arabinose to xylose end-groups of 11 : 1 that the majority of arabinose residues in the barley araboxylan must be attached directly to the backbone of xylose residues as in structure (I).

[7] Hirst, Hough, and Jones, *J.*, 1949, 928.

It is clear from these results that the barley-flour araboxylan is similar to other polysaccharides of the xylan group [8] in containing chains of 1 : 4-linked β-D-xylopyranose residues to which are attached single-unit L-arabofuranose side-chains. The polysaccharide resembles most closely the araboxylans from wheat [3] and rye [9] flour, differing only in that some of the singly-branched xylose residues carry arabinose residues attached to $C_{(2)}$ whereas in other xylans arabinose residues are linked to $C_{(2)}$ only in the case of doubly-branched xylose residues carrying a substituent at $C_{(3)}$ also. It is of particular interest that within the general structural pattern common to the various xylans from land plants [8] the araboxylans from cereal grains form a group of substances which differ from the typical xylans of lignified tissues in containing a higher proportion of arabinose but no glucuronic acid residues often found in the latter group. Barley-flour araboxylan and barley-husk hemicellulose [6] provide an example of polysaccharides from the same plant which differ in detailed chemical structure and probably also in biological function.

## Experimental

Paper chromatography was carried out on Whatman No. 1 filter paper, with the upper layers of the following solvent systems (v/v): (A) butan-1-ol–benzene–pyridine–water (5 : 1 : 3 : 3); (B) butan-1-ol–ethanol–water (4 : 1 : 5); (C) benzene–ethanol–water (169 : 47 : 15). Paper ionophoresis was in borate buffer at pH 10. Optical rotations were observed at 18° ± 2°. Methylated sugars were demethylated with hydrobromic acid.[10]

*Extraction and Fractionation of Barley Gum.*—Barley (Carlsberg variety, harvested in 1953) was passed through an automatic polishing machine to remove husks, and the grain was ground to a fine flour. Barley flour (8 kg.), previously extracted with boiling ethanol–water (4 : 1) to inactivate enzymes and remove soluble sugars, waxes, and colouring matter, was extracted with water at 40° according to Preece and Mackenzie's [1] procedure and gave barley gum (14 g.; 0·18% of the grain). Precipitation of the gum from aqueous solution by the addition of ammonium sulphate afforded fractions (1) (8 g.; mainly glucan precipitated with 20% ammonium sulphate) and (2) (5·7 g.; precipitated with 30% and 40% ammonium sulphate). Fraction (2) had $[\alpha]_D$ −125° ± 5° (*c*, 0·2 in N-sodium hydroxide) and quantitative chromatography of the hydrolysate [11] showed xylose (49%), arabinose (32%), and glucose (19%). Fraction (2) (5 g.) was dispersed in formamide (65 ml.), and pyridine (195 ml.) was added and then acetic anhydride (100 ml.) slowly with stirring during 4 hr. The mixture was stirred for 2 days at room temperature and poured into water (2 l.) to give acetylated polysaccharide (6·4 g.), which was exhaustively extracted with acetone leaving a residue (0·21 g.). Addition of light petroleum (b. p. 60—80°; 250 ml.) to the acetone extract (500 ml.) gave acetate (A) (3·8 g.), $[\alpha]_D$ −107° (*c*, 1·0 in pyridine) [Found: OAc, 34·3%], and concentration of the supernatant liquid gave acetate (B) (2·2 g.), $[\alpha]_D$ −39° (*c* 1·0 in pyridine) [Found: OAc, 35·5%]. A sample of acetate (A) (0·5 g.) was deacetylated by Zemplen and Pacsu's [12] method to give polysaccharide (0·266 g.), $[\alpha]_D$ −104° (*c* 0·6 in N-sodium hydroxide), hydrolysis and quantitative chromatography [11] showing xylose (59%), arabinose (37%), and glucose (4%). A sample of acetate (B) was hydrolysed directly and quantitative chromatography showed xylose (29%), arabinose (27%), and glucose (44%).

*Methylation.*—Acetylated polysaccharide (A) (2·9 g.) was methylated by successive treatments with methyl sulphate and sodium hydroxide, and fractional precipitation of the product from chloroform by the addition of light petroleum (b. p. 60—80°) gave fractions (C) (1·177 g.), $[\alpha]_D$ −140° (*c* 0·5 in chloroform) (Found: OMe, 37·3%), and (D) (0·412 g.), $[\alpha]_D$ −134° (*c* 0·5 in chloroform) (Found: OMe, 37·7%). Samples of (C) and (D) were hydrolysed, and chromatography showed tri-*O*-methylarabinose, di- and mono-*O*-methylxylose, and xylose; small amounts of tri-*O*-methylglucose were also detected in the hydrolysate from (D), but not in this experiment in that from (C). Further methylation of fraction (C) gave methylated araboxylan

[8] Hirst, *J.*, 1955, 2974; Aspinall and Schwarz, *Ann. Reports*, 1955, **52**, 261; D. C. C. Smith, *ibid.*, 1956, **53**, 257.
[9] Aspinall and Sturgeon, *J.*, 1957, 4469.
[10] Hough, Jones, and Wadman, *J.*, 1950, 1702.
[11] Flood, Hirst, and Jones, *J.*, 1948, 1679.
[12] Zemplen and Pacsu, *Ber.*, 1929, **62**, 1613.

(0·94 g.), $[\alpha]_D$ −137° (*c* 0·6 in chloroform) (Found: OMe, 38·2%). Hydrolysis of a sample of methylated araboxylan, and quantitative chromatography [7] of the hydrolysate showed the relative amounts of pentose sugars to be: tri-*O*-methylarabinose, 4·1 parts, di-*O*-methylxylose, 3·6 parts, mono-*O*-methylxylose, 1 part, and xylose 1·3 parts.

*Hydrolysis of Methylated Araboxylan and Separation of Methylated Sugars.*—Methylated araboxylan (0·9 g.) was hydrolysed successively with boiling methanolic 3% hydrogen chloride (100 ml.) for 3·5 hr. and 0·5N-hydrochloric acid (100 ml.) at 100° for 3 hr. After neutralisation with silver carbonate, concentration gave a syrupy mixture of methylated sugars (0·72 g.) which was fractionated on cellulose (40 × 2 cm.) with light petroleum (b. p. 100—120°)–butan-1-ol (7 : 3) saturated with water, and butan-1-ol partly saturated with water, as eluants, to give eight fractions.

*Fraction* 1. The syrup (197 mg.) had $[\alpha]_D$ −35° (*c* 0·5 in water) (Found: OMe, 47·9. Calc. for $C_8H_{16}O_5$: OMe, 48·4%), and was chromatographically indistinguishable from 2 : 3 : 5-tri-*O*-methyl-L-arabinose in solvents B and C. Demethylation gave arabinose. The sugar was characterised by conversion into 2 : 3 : 5-tri-*O*-methyl-L-arabonamide, m. p. and mixed m. p. 133—135°.

*Fraction* 2. Chromatography in solvent B showed the syrup (28 mg.) to contain 2 : 3 : 5-tri-*O*-methylarabinose and tri-*O*-methylglucose in the approximate ratio of 3 : 1. Chromatography in solvent C showed that a trace of 2 : 3 : 4-tri-*O*-methylxylose was also present. Demethylation gave arabinose, glucose, and a trace of xylose.

*Fraction* 3. Chromatography in solvent B showed the syrup (43 mg.) to contain tri-*O*-methylglucose and 2 : 3-di-*O*-methylxylose. The optical rotation ($[\alpha]_D$ +44°, in water) was consistent with the presence of tri-*O*-methylglucose (2 : 3 : 6- and 2 : 4 : 6-trimethyl ethers have $[\alpha]_D$ +70°, in water [13]) and 2 : 3-di-*O*-methyl-D-xylose ($[\alpha]_D$ +23° in water [15]) in the ratio 1 : 1·2.

*Fraction* 4. The chromatographically pure syrup (154 mg.) had $[\alpha]_D$ +25° (*c* 0·7 in water) (Found: OMe, 33·5. Calc. for $C_7H_{14}O_5$: OMe, 35·0%), and gave xylose on demethylation. The sugar was characterised as 2 : 3-di-*O*-methyl-D-xylose by conversion into the aniline derivative, m. p. and mixed m. p. 123—124°.

*Fraction* 5. The syrup (45 mg.) travelled on the chromatogram in solvent B at the same rate as 2- and 3-*O*-methyl-D-xylose, and ionophoresis showed both methyl ethers to be present (Found: OMe, 18·6. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). Demethylation gave xylose. The optical rotation ($[\alpha]_D$ +29°, in water) was consistent with the presence of 2-*O*-methyl-D-xylose ($[\alpha]_D$ +17°) [15] and 3-*O*-methyl-D-xylose ($[\alpha]_D$ +35°) [16] in the ratio 2 : 1. The syrupy mixture of methyl pyranosides, prepared by refluxing the syrup with dry methanolic hydrogen chloride, consumed 0·76 mol. of periodate (spectrophotometric determination [17]).

*Fraction* 6. The syrup (9 mg.) contained an unknown sugar *a* ($R_G$ 0·30 in solvent B) and xylose in the approximate ratio of 2 : 1. Hydrolysis of sugar *a* gave di- and mono-*O*-methylxylose in about equal amounts. In subsequent calculations 3 mg. of each were added to the quantities of xylose, mono-, and di-*O*-methylxylose isolated in pure fractions.

*Fraction* 7. Chromatographically pure D-xylose (45 mg.) crystallised and had m. p. and mixed m. p. 139—142°, $[\alpha]_D$ +22° (equil.) (in water).

*Fraction* 8. Chromatography showed the syrup (23 mg.) to contain xylose and a number of slower-moving components. The syrup was hydrolysed and quantitative estimation indicated the presence in the mixture of residues of xylose (13 mg.) and mono- (4 mg.) and di-*O*-methylxylose (6 mg.). In subsequent calculations these quantities were added to the appropriate fractions.

The quantities of sugars isolated from the hydrolysis of the methylated araboxylan indicate their presence in the following molar percentages: 2 : 3 : 5-tri-*O*-methyl-L-arabihose (39%), 2 : 3-di-*O*-methyl-D-xylose (36%), mono-*O*-methyl-D-xylose (11%), and D-xylose (14%).

*Partial Hydrolysis of Methylated Araboxylan.*—Methylated araboxylan (fraction D, 56 mg.) was dissolved in methanol (5 ml.), 0·2N-hydrochloric acid (5 ml.) was added, and the mixture was refluxed for 4 hr. The solution was neutralised with Amberlite resin IR-4B, filtered, and freeze-dried. The residue was exhaustively extracted with boiling light petroleum

[13] See Bourne and Peat, *Adv. Carbohydrate Chem.*, 1950, **5**, 145.
[14] Chanda, Percival, and Percival, *J.*, 1952, 260.
[15] Percival and Willox, *J.*, 1949, 1608.
[16] White, *J. Amer. Chem. Soc.*, 1953, **75**, 257, 4692.
[17] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.

XUM

(b. p. 60—65°), and chromatographic examination of the extract (4·5 mg.) showed 2 : 3 : 5-tri-*O*-methylarabinose and a trace of 2 : 3-di-*O*-methylxylose. The residual methylated polysaccharide was remethylated with methyl iodide and silver oxide and yielded methylated degraded araboxylan (36 mg.) (Found: OMe, 38·9%). The methylated polysaccharide was hydrolysed as described previously, the tri-*O*-methylpentose fraction was resolved chromatographically by solvent C, and quantitative estimation by Pridham's [18] method showed 2 : 3 : 5-tri-*O*-methylarabinose and 2 : 3 : 4-tri-*O*-methylxylose to be present in the ratio of 11 : 1. On treatment with *p*-anisidine hydrochloride the sugars gave products having absorption maxima at 390 and 500 mμ, respectively, and it was shown that at these wavelengths and for weights of sugar from 10—40 μg. the absorption was directly proportional to the quantity of sugar.

The authors thank Professor E. L. Hirst, F.R.S., for his interest and advice. This work was carried out under the auspices of the Brewing Industry Research Foundation, to whom the authors are indebted for the award of a scholarship (to R. J. F.). They also thank the Rockefeller Foundation and the Earl of Moray Endowment for grants.

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF EDINBURGH. [*Received, October 7th*, 1957.]

[18] Pridham, *Analyt. Chem.*, 1956, **28**, 1967.

---

## 125. *Metal Derivatives of Conjugated Dienes. Part I. Butadiene- and cycloHexadiene-iron Tricarbonyls.*

By B. F. HALLAM and P. L. PAUSON.

*cyclo*Hexa-1 : 3-diene reacts with iron carbonyl in the same manner as butadiene.[1] The properties of the resultant diene–iron tricarbonyls have been studied and their structures are discussed.

THE formation of butadieneiron tricarbonyl, $C_4H_6Fe(CO)_3$, from butadiene and iron pentacarbonyl was first reported by Rheilen, Gruhl, Hessling, and Pfrengle [1] in 1930 and later formed the subject of a patent by Veltman.[2] However, the efforts of the former authors to extend the reaction to other dienes led only to ill-defined products of the approximate composition $(C_5H_8)_2Fe(CO)_3$ and $(C_5H_8)_3Fe(CO)_3$ from isoprene and $(C_6H_{10})_2Fe(CO)_3$ from dimethylbutadiene and no further work on this interesting group of compounds has appeared. The present reinvestigation, stimulated by our interest in the reaction of iron carbonyls with *cyclo*pentadiene,[3,4] was initiated to obtain evidence on the structure of butadieneiron tricarbonyl.

Rheilen *et al.*[1] tentatively considered structure (I) for this compound. However, it appears extremely unlikely that even a " chelated " dialkyl of iron could be so remarkably stable as this substance. Its thermal stability is evident from its formation at 100—150° and from the fact that repeated distillation leaves it unchanged. We have kept a sample in a refrigerator for more than a year. The compound can be recovered unchanged from its solutions in pyridine, glacial acetic acid, and even concentrated sulphuric acid. It is likewise unaffected by hydrogen in the presence of Adams catalyst and by boiling with maleic anhydride in benzene solution for 48 hr.

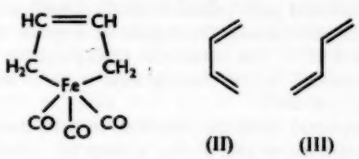
Although a number of alkyl derivatives of iron [4,5] and other transition-metal carbonyls [6,7] have been described, the metal atom in all these may be regarded as attaining

[1] Rheilen, Gruhl, Hessling, and Pfrengle, *Annalen*, 1930, **482**, 161.
[2] Veltman, U.S.P. 2,409,167; *Chem. Abs.*, 1947, **41**, 595.
[3] Hallam, Mills, and Pauson, *J. Inorg. Nuclear Chem.*, 1955, **1**, 313.
[4] Hallam and Pauson, *J.*, 1956, 3030.
[5] Piper and Wilkinson, *Chem. and Ind.*, 1955, 1296; *Naturwiss.*, 1956, **43**, 15; *J. Inorg. Nuclear Chem.*, 1956, **3**, 104.
[6] Fischer, Hafner, and Stahl, *Z. anorg. Chem.*, 1955, **282**, 47.
[7] Closson, Kozikowski, and Coffield, *J. Org. Chem.*, 1957, **22**, 598.

the electronic configuration of the next inert gas. Thus, by analogy to the alkylmanganese pentacarbonyls,[7] it may prove possible to prepare dialkyliron tetracarbonyls, $R_2Fe(CO)_4$, derived from iron hydrocarbonyl. However, a tricarbonyl $R_2Fe(CO)_3$ such as (I) would have only 34 electrons about the iron atom and would most probably be paramagnetic, whereas butadieneiron tricarbonyl is diamagnetic.

Further, we have shown that ozonolysis of this compound yields some formaldehyde and that reduction by lithium aluminium hydride yields some butadiene. Although these observations could be explained by the assumption that complete rupture of (I) to yield butadiene is the first step in each case, they are much more consistent with formulations in which the conjugated diene system remains essentially intact. This view is confirmed by the spectra of butadieneiron tricarbonyl. Its ultraviolet spectrum has an intense maximum at 211 mμ (in ethanol) compared with the maximum of butadiene gas at 217 mμ.[8] Its infrared spectrum includes a band at 1464 cm.$^{-1}$ which may be analogous to the band occurring at 1475 cm.$^{-1}$ in the spectrum of the bridged butadiene–platinum complex $K_2[C_4H_6(PtCl_3)_2],H_2O$ and attributed to a C=C stretching frequency lowered by conjugation and co-ordination to the metal.[9]

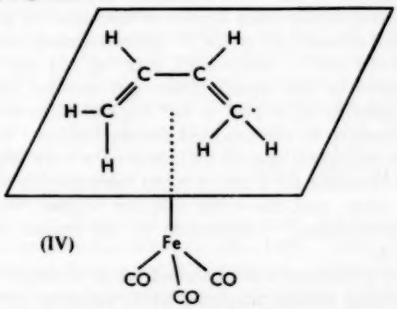
We believe that the rejection of structure (I) leaves only one reasonable arrangement for the molecule, *i.e.*, that in which the hydrocarbon attains a planar (or nearly planar) configuration and in which the π-electrons are utilised in bonding. There are two ways of arranging a butadiene molecule in a plane: the " cisoid " form (II) and the " transoid " form (III). To distinguish between these we examined the reaction of iron pentacarbonyl with *cyclo*hexadiene. It yields *cyclo*hexadieneiron tricarbonyl, almost identical in spectral and other properties with the butadiene compound and therefore presumably analogous in structure. Since *cyclo*hexadiene must be cisoid and cannot deviate greatly from planarity, the same arrangement is made highly probable for butadieneiron tricarbonyl. We therefore propose structure (IV) for this compound. In this structure the iron atom lies outside the plane defined by the hydrocarbon portion and is roughly equidistant from the four carbon atoms of the butadiene; the iron atom probably forms a tetrahedron with the three carbonyl groups. It is hoped to confirm this molecular geometry by means of the *X*-ray crystallographic studies now in progress.




(I)



(II) (III)




(IV)

The nature of the bonding between the iron atom and the conjugated diene must be considered, bearing in mind the distribution of the π-orbitals over all four carbon atoms of the latter as the arrangement of lowest energy. We believe that this will lead to a metal–carbon bond of a type more closely related to that in ferrocene,[10] in the benzene–metal compounds (such as dibenzenechromium[11] and dimesityleneferrous salts[12]), and that postulated for the hypothetical *cyclo*butadiene–metal compounds,[13] than to that in

[8] Smakula, *Angew. Chem.*, 1934, **47**, 657.
[9] Chatt and Duncanson, *J.*, 1953, 2939.
[10] Pauson, *Quart. Reviews*, 1955, **9**, 391.
[11] Fischer and Hafner, *Z. Naturforsch.*, 1955, **10b**, 665; *Z. anorg. Chem.*, 1956, **286**, 146.
[12] Fischer and Böttcher, *Chem. Ber.*, 1956, **89**, 2397.
[13] Longuet-Higgins and Orgel, *J.*, 1956, 1969.

XUM

the chelate complexes of non-conjugated diolefins such as *cyclo*octadiene.[14,15] This may account for the existence of butadiene complexes of iron in spite of the fact that neither mono-olefins nor non-conjugated dienes have been found to yield complexes with any of the metals from the first row of Group VIII. Thus, according to our views, the conjugated nature of the diene system is an essential feature for the formation of compounds like butadieneiron tricarbonyl, and unconjugated diolefins would not be expected to form iron derivatives of comparable stability or even of comparable type. This consequence is being tested further, as is also the ability of the other transition metals to yield analogous compounds.

The successful preparation of a *cyclo*hexadieneiron tricarbonyl suggested that even *cyclo*pentadiene derivatives might yield analogous compounds provided they bore two substituents on the methylene carbon atom. Two such derivatives were tested, but both reacted with rearrangement of the carbon skeleton. These results are described in the following paper.

Several attempts have also been made to replace either the hydrocarbon or the carbonyl function directly. When the butadiene derivative is heated with *cyclo*pentadiene, complete displacement of the former hydrocarbon occurs and di*cyclo*pentadienyldiiron tetracarbonyl[3] is formed. When however, butadieneiron tricarbonyl is caused to react with *cyclo*pentadienylsodium a new product is formed which retains at least one butadiene residue, but which has bands in the infrared carbonyl stretching region very similar to those of di*cyclo*pentadienyldi-iron tetracarbonyl. It is thus clearly at least binuclear, with both bridging and non-bridging carbonyl groups. Its complete structure is under investigation.

All attempts to dehydrogenate *cyclo*hexadieneiron tricarbonyl to a benzene–iron derivative have failed.

## Experimental

Alumina used for chromatography was Spence's Grade H deactivated by exposure to air for 6 hr. Ligroin refers to the solvent of b. p. 40—60°.

*Butadieneiron Tricarbonyl.*—This was prepared in an autoclave according to the method of Rheilen *et al.*[1] The product crystallised partially during distillation at 48°/0·06 mm. Recrystallisation from ligroin or methanol at −78° afforded pale yellow crystals of butadieneiron tricarbonyl, m. p. 19°.* Infrared max. in the carbonyl stretching region at approx. 2051 and 1978 cm.$^{-1}$; ultraviolet max. at 211 mμ (log ε 4·36). The magnetic susceptibility was measured in the liquid phase and showed the compound to be diamagnetic with a molar susceptibility of $-78{\cdot}4 \times 10^{-6}$ c.g.s.u. at room temp. (*ca.* 24°).

Contrary to the reported decomposition,[1] the compound (0·22 g.) dissolved in cold concentrated sulphuric acid (2 ml.) with only very slight evolution of gas, giving a deep red solution. After standing for 2 hr. at room temperature this solution was poured on ice (20 g.), extracted with ether, and the ether solution washed with sodium hydrogen carbonate solution, dried, and evaporated. Distillation of the residue at 76°/20 mm. afforded unchanged tricarbonyl (0·15 g.).

No hydrogen was absorbed when a solution of the carbonyl (0·39 g.) in ethanol (25 ml.) containing Adams platinum oxide catalyst (20 mg.) was stirred in a hydrogen atmosphere.

Both starting materials were largely recovered unchanged when a solution of butadieneiron tricarbonyl (0·97 g.) and maleic anhydride (0·49 g.) in benzene (15 ml.) was kept at room temp. for 6 days and then heated under reflux for 48 hr. Some decomposition of the carbonyl occurred during this period.

*Reduction of Butadieneiron Tricarbonyl with Lithium Aluminium Hydride.*[16]—The carbonyl (0·054 g.) was added at 0° to a solution of lithium aluminium hydride (0·2 g.) in anhydrous

* The crystalline nature of this product was independently observed some years ago by Dr. H. W. B. Reed of Imperial Chemical Industries Limited (personal communication).

[14] Chatt and Venanzi, *Nature*, 1956, **177**, 853.
[15] Chatt, Vallarino, and Venanzi, *J.*, 1957, 2496.
[16] Zeiss and Tsutsui, Technical Report No. 4 under Contract No. DA–19–059–ORD–1494 between the Office of Ordnance Research, U.S. Army, and Yale University, June 1955.

XUM

tetrahydrofuran (200 ml.), and the mixture stored at 0° for 6 hr. in a tightly stoppered flask. Water (1 ml.) was then rapidly added, and the mixture warmed gently on a water-bath. The temperature was kept just below the b. p., the reaction flask being connected during this period to a trap containing ethanol at −78°. The ultraviolet spectrum of this alcoholic solution showed a strong peak at 219 mμ corresponding in intensity to the presence of *ca.* 1 mg. (7% yield) of butadiene.

*Ozonolysis of Butadieneiron Tricarbonyl.*—The carbonyl (0·4 g.), dissolved in glacial acetic acid (50 ml.), was treated with a stream of ozone (3·3%; 350 ml. of oxygen per min.) at room temp. for 30 min. The resultant solution was combined with the water (50 ml.) through which the effluent gases had been passed and distilled with steam over zinc dust (2 g.). From the distillate (150 ml.), neutralised with sodium hydroxide, formaldehyde was precipitated as the dimedone derivative (72 mg.).

*Attempted Phenylation of Butadieneiron Tricarbonyl.*—Only unchanged tricarbonyl (50—60%, isolated by chromatography of the reaction products on alumina) was recovered when this compound (1 g.) was allowed to react with *N*-nitrosoacetanilide (0·82 g.) in *cyclo*hexane (50 ml.) at room temp. (7 hr.) and 50° (1 hr.), or when it (1·94 g.) was treated with benzenediazonium sulphate (from 1 ml. of aniline) in glacial acetic acid (75 ml.) at room temp. (14 hr.).

*Reaction of Butadieneiron Tricarbonyl with* cyclo*Pentadiene.*—The carbonyl (1·94 g.) and *cyclo*pentadiene (5 ml.; freshly distilled) were heated under carbon dioxide in an autoclave at 150° for 5 hr. Chromatography of a benzene solution of the product on alumina and crystallisation from ligroin yielded purple crystals (309 mg.). Although further crystallisation from the same solvent or from aqueous pyridine as well as sublimation under a high vacuum failed to raise the m. p. of this product above 170—172°, its infrared spectrum was identical with that of di*cyclo*pentadienyldi-iron tetracarbonyl and a mixed m. p. with the latter (m. p. 192°) was undepressed (176—180°).

*Reaction of Butadieneiron Tricarbonyl with* cyclo*Pentadienylsodium.*—A solution of the carbonyl (1·94 g.) in tetrahydrofuran (15 ml.) was added to *cyclo*pentadienylsodium prepared from *cyclo*pentadiene (2 ml.) and sodium (0·26 g.) in the same solvent (25 ml.). After being heated under reflux on a steam-bath for 7 hr. in a current of nitrogen, the solution was evaporated *in vacuo* and the residual red oil was partitioned between ether and water. The yellow aqueous layer was very unstable in air and the product contained in it has not yet been characterised. The purple ether layer was evaporated, leaving an oil which was dissolved in a minimum amount of benzene and chromatographed on alumina. Ligroin eluted a yellow oil (0·33 g.), b. p. 62°/17 mm., which decomposed completely when kept in an evacuated desiccator for a few hours. This was followed by a small amount (*ca.* 20 mg.) of a second unstable, orange oil, eluted by the same solvent. A brownish-purple band was then eluted with benzene and, after evaporation of the solvent, the residue, dissolved in acetone, deposited purple crystals (0·41 g.) on addition of ligroin. Recrystallisation from ligroin afforded the pure product, m. p. 97° (decomp.; vac.) [Found: C, 53·8, 52·7; H, 4·4, 4·2; O, 16·4, 16·9%; *M*, 377 (cryoscopic in benzene)]. The compound is diamagnetic: $\chi_{mole} = -124{\cdot}7 \times 10^{-6}$ c.g.s.u. It has infrared max. in the carbonyl stretching region at approx. 2029, 1971, 1817, and 1764 cm.$^{-1}$ and ultraviolet max. at 211 and 343 mμ (log ε 4·54 and 3·96).

cyclo*Hexadieneiron Tricarbonyl.*—*cyclo*Hexa-1 : 3-diene (12 g.) and iron pentacarbonyl (20 g.) were heated under carbon dioxide in an autoclave for 24 hr. at 135—140°. The resulting yellow liquid was dissolved in acetone and filtered from insoluble material. After removal of the solvent and of excess of iron pentacarbonyl, cyclo*hexadieneiron tricarbonyl* distilled at 96°/12 mm. as a yellow liquid (4·7 g.), f. p. 8—9° (Found: C, 50·5, 50·3; H, 4·2, 4·0; O, 21·8, 21·9. $C_9H_8O_3Fe$ requires C, 49·1; H, 3·7; O, 21·8%). Infrared max. in the carbonyl stretching region at approx. 2066 and 1978 cm.$^{-1}$; ultraviolet max. at 207 mμ (log ε 4·36). The consistently high C and H analyses obtained for this compound presumably result from difficulty in separating it completely from excess of *cyclo*hexadiene; they are, however, far below those expected for a 2 : 1 ratio of hydrocarbon : iron as found with isoprene and dimethylbutadiene.[1]

The authors are indebted to Dr. H. W. B. Reed of I.C.I. Ltd. for supplies of butadiene. They are grateful to Dr. H. Geyer for performing the oxygen analyses. They thank the University of Sheffield for the award of a Henry Ellison Fellowship (to B. F. H.).

THE UNIVERSITY, SHEFFIELD, 10. [*Received, July 19th*, 1957.]

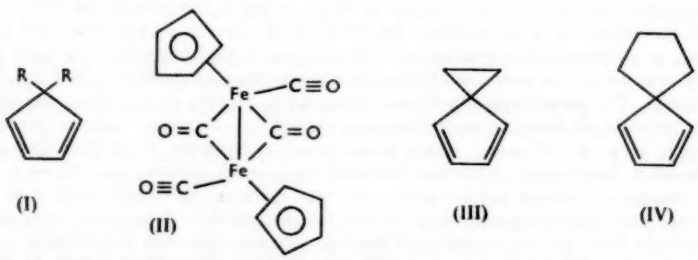
XUM

## 126. *Ferrocene Derivatives. Part IV.*[1] *Indenyl- and Tetrahydroindenyl-iron Carbonyls.*

By B. F. Hallam and P. L. Pauson.

The structures of *spiro*[2 : 4]hepta-1 : 3-diene and *spiro*[4 : 4]nona-1 : 3-diene have been confirmed. Both hydrocarbons rearrange during their reactions with iron pentacarbonyl. The *spiro*nonadiene yields bistetrahydroindenyldi-iron tetracarbonyl (VII), which is converted by pyrolysis into bistetrahydroindenyliron. Indene reacts with iron pentacarbonyl to yield di-indenyldi-iron tetracarbonyl which has been reduced to the same tetrahydro-derivative (VII).

In connection with the study of butadieneiron tricarbonyl (preceding paper) it appeared of interest to determine whether 5 : 5-disubstituted *cyclo*pentadienes (I) would give analogous products with iron pentacarbonyl. The reaction occurs (with butadiene and related dienes) under conditions under which *cyclo*pentadiene itself yields di*cyclo*pentadienyldi-iron tetracarbonyl (II) [1] in which the metal–ring bonding is of the ferrocene type. This cannot be attained with the *gem.*-disubstituted derivatives (I) (except with rearrangement of the carbon skeleton). Hence it might be expected that *cyclo*pentadienes of this type (I) would form products having the (presumably less energetically favourable) type of bonding found in the butadiene complex. In practice this expectation was not realised, the two compounds studied, *spiro*[2 : 4]hepta-1 : 3-diene (III) [2] and *spiro*[4 : 4]nona-1 : 3-diene (IV),[3] reacting exclusively with rearrangement to yield binuclear tetracarbonyls analogous to (II).

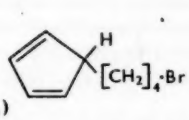



(I) (II) (III) (IV)

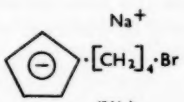
The spirans (III) and (IV) were selected because, among the few known simple *gem.*-disubstituted *cyclo*pentadiene derivatives, they appeared most readily accessible, being obtained by direct alkylation of *cyclo*pentadiene, without danger of contamination from lower or higher homologues. Unfortunately, however, their structures—particularly that of (IV)— had not previously been rigidly established and it was therefore necessary to do this by degradative methods. The *spiro*nonadiene (IV) is obtained by reaction of *cyclo*pentadiene with sodamide and tetramethylene bromide in liquid ammonia. This alkylation must proceed in two stages. The first reaction of the dihalide with *cyclo*pentadienylsodium leads to the intermediate (Va) which then reacts with more sodamide to yield its salt (Vb). As the negative charge in the latter is not localised on any particular ring carbon atom, it could cyclise either to (IV) or to an isomer having the indene skeleton, *e.g.*, (VI), or to a mixture of the two. The only evidence previously advanced [3] in support of the formulation as (IV) was comparison of the boiling point and refractive index of its tetrahydro-derivative with the data recorded for authentic *spiro*[4 : 4]nonane. Such comparison does not appear to rule out structures such as (VI) for all or part of the material.

[1] Part III, *J.*, 1956, 3030.
[2] Levina, Mezentsova, and Lebeda, *Zhur. obshchei Khim.*, 1955, **29**, 1097.
[3] Levina and Tantsireva, *Doklady Akad. Nauk S.S.S.R.*, 1953, **89**, 697.

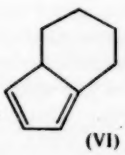
Similarly, no evidence had been presented to rule out alternative structures for (III) and, although in this case the fused *bicyclo*[3 : 2 : 0]heptadiene structure appears *a priori* less likely, it was decided to reinvestigate both compounds. Ozonolysis converted (III) and (IV) into *cyclo*propane-1 : 1-dicarboxylic and *cyclo*pentane-1 : 1-dicarboxylic acids respectively, but in poor yields. In the case of the *spiro*nonadiene (IV), permanganate oxidation gave improved results. Fortunately, the maleic anhydride adducts [2,3] could be prepared in over 90% yield in both cases, proving the essential homogeneity of the hydrocarbons and hence—in conjunction with the oxidative evidence—that at least 90% of each of the hydrocarbons had the structure assigned to it.




(Va)



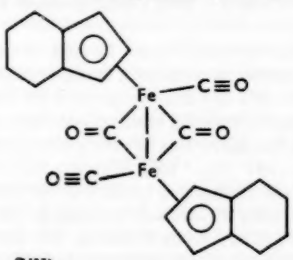

(Vb)



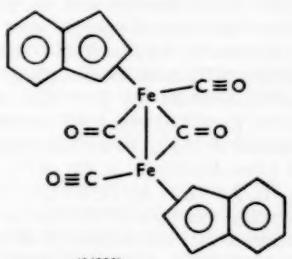
(VI)

When the *spiro*heptadiene (III) was heated with iron pentacarbonyl it afforded mainly a purple gum, resembling the tetracarbonyl (II), but clearly polymeric. A crystalline fraction (1·6%) was identified as the diethyl derivative of (II) by analysis and infrared spectrum. Both products are best understood as resulting from the opening of the *cyclo*propane ring of (III). This would yield mainly vinyl*cyclo*pentadiene and it is here postulated that the major polymeric product is derived from this hydrocarbon. Ethyl*cyclo*pentadiene (or the ethyl*cyclo*pentadienyl radical) can clearly arise by partial disproportionation of the radical intermediate of this ring fission. However, the yield of the crystalline product was too low to exclude the possibility that sufficient ethyl*cyclo*pentadiene for its formation was present in the starting material (III) [as a result of reduction of the intermediate bromoethyl*cyclo*pentadiene during the liquid ammonia reaction].

More clear-cut results were obtained with the *spiro*nonadiene (IV) which reacted with iron pentacarbonyl to give bistetrahydroindenyldi-iron tetracarbonyl (VII) in 39% yield. Since the starting material is at least 91% pure (IV), the formation of (VII) can only be attributed to rearrangement of (IV) during the reaction and not to the possible presence of traces of tetrahydroindenes in the starting material. The possibility remains that this rearrangement of the spiran (IV) occurs independently of its reaction with iron pentacarbonyl. In an attempt to test this, a sample of the hydrocarbon (IV) was heated under the reaction conditions. However, the main product was a new hydrocarbon of double the molecular weight and it is not known whether this is a dimer of the spiran (IV) itself or a dimer of a rearrangement product.




(VII)




(VIII)

The structure of the tetracarbonyl (VII) was proved both by conversion into the known bistetrahydroindenyliron [4] on pyrolysis and by an independent synthesis from indene. The latter reacted with iron pentacarbonyl in the same fashion as *cyclo*pentadiene, yielding di-indenyldi-iron tetracarbonyl (VIII). Surprisingly, this compound is comparable in

[4] Fischer and Seus, *Z. Naturforsch.*, 1954, **9b**, 386.

XUM

stability with its *cyclo*pentadiene analogue (II), whereas di-indenyliron is very unstable compared with ferrocene. This indene compound (VIII) was smoothly hydrogenated to the octahydro-derivative (VII) at room temperature and pressure provided a large excess of platinic oxide catalyst was used. This reduction closely parallels that of di-indenyliron to its octahydro-derivative.[4] The resistance, not only of the *cyclo*pentadiene ring, but of the whole system (II), to these hydrogenation conditions was separately demonstrated before this series of reactions was undertaken. Reduction of (VIII) to (VII) incidentally proves that the indene molecules in (VIII) are linked to the metal atoms through the five-membered and not (as in dimesityleneiron salts [5]) through the benzenoid rings.

The absorption of (VII) in the carbonyl stretching region of the infrared is almost indistinguishable from that of (II), but that of (VIII) shows significant differences, the position of the main bridging carbonyl band being shifted appreciably towards higher wavelength. This observation stresses the extent to which relatively remote parts of a molecule can affect such specific group frequencies.

## Experimental

spiro[2 : 4]*Hepta*-1 : 3-*diene*.—Following Levina *et al.*[2] *cyclo*pentadiene (50 g.) was added during 30 min. to a solution of sodium (35 g.) in liquid ammonia (1500 ml.) under reflux. Then 1 : 2-dibromoethane (144 g.) was run in during 40 min., and, after a further 1·5 hours' stirring the reaction mixture was treated with ether (200 ml.) and water (400 ml.). The ether layer, combined with ether extracts of the aqueous layer, was washed with water and dilute hydrochloric acid, dried ($Na_2SO_4$), and evaporated. Fractional distillation of the residue yielded the *spiro*heptadiene (III) (13·2 g.), b. p. 45—47°/93 mm., $n_D^{20}$ 1·5070 (lit.,[2] b. p. 57°/100 mm., $n_D^{20}$ 1·5078).

This spiran (0·35 g.) reacted exothermically with maleic anhydride (0·37 g.) dissolved in benzene (4 ml.). After standing for 1 hr. at room temp. this solution was evaporated, and the residue crystallised from ether–ligroin (b. p. 40—60°), yielding the adduct (0·65 g.; 90%), m. p. 97—98° (lit.,[2] m. p. 97°).

*Ozonolysis of the Spiran* (III).—A stream of ozone (3·3%; 350 ml. of oxygen per min.) was passed for 3·5 hr. through a solution of the spiran (III) (2·76 g.) in ethyl acetate (50 ml.) at −78°. Glacial acetic acid (75 ml.) was then added, and the solution evaporated *in vacuo* to approx. 20 ml. It was now added to a mixture of hydrogen peroxide (20 ml.; 100-vol.), concentrated sulphuric acid (0·75 ml.), and water (30 ml.), cautiously warmed to 40°, and kept at this temperature for 1 hr. After standing at room temp. for 36 hr. the solution was evaporated to small bulk under reduced pressure and the residue, acidified with dilute hydrochloric acid, extracted continuously with ether for 24 hr. Evaporation of the dried ($Na_2SO_4$) ether solution and crystallisation of the residue from chloroform–ligroin (b. p. 40—60°) yielded *cyclo*propane-1 : 1-dicarboxylic acid, m. p. 134—136° (1·33 g.; 34%), undepressed by an authentic specimen; the infrared spectra were identical.

spiro[4 : 4]*Nona*-1 : 3-*diene* (IV).—This spiran was prepared (see Levina *et al.*[3]) like its lower homologue (III) from sodium (20 g.) in liquid ammonia (500 ml.), *cyclo*pentadiene (28 g.), and 1 : 4-dibromobutane (80 g.). The product (IV) (5·7 g.) had b. p. 44—46°/22 mm., $n_D^{20}$ 1·4817 (lit.,[3] b. p. 52°/10 mm.; $n_D^{20}$ 1·4790). A sample (0·20 g.) reacted exothermically with maleic anhydride (0·163 g.) in benzene (2 g.), yielding the adduct as silvery white plates [0·33 g. 91%; from ether–ligroin (b. p. 40—60°)], m. p. 100—101° (lit.,[3] 98°) (Found: C, 71·2; H, 6·8. Calc. for $C_{13}H_{14}O_3$: C, 71·5; H, 6·5%). The m. p. was unchanged on further recrystallisation. The homogeneity was further verified by hydrolysis with 2N-sodium hydroxide (20 ml.) for 1 hr. on a steam-bath; the adduct (0·26 g.) was completely hydrolysed to the corresponding *dicarboxylic acid* (0·277 g.), m. p. 180° (decomp.), isolated by acidification, filtration, and crystallisation from acetone at low temperature (Found: C, 65·7, 65·9; H, 6·7, 6·9. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%). A pure sample of this acid (0·1 g.) was reconverted into the anhydride by refluxing (1·5 hr.) with acetyl chloride (2 ml.), evaporation, and crystallisation from ether–ligroin. The product (83 mg.) had m. p. 98—99°, undepressed by admixture with the original adduct.

[5] Fischer and Böttcher, *Chem Ber.* 1956, **89**, 2397.

*Ozonolysis of the Spiran* (IV).—Ozonolysis of the *spiro*nonadiene (IV) (2·4 g.) was carried out for 2·5 hr. under the same conditions as described for the *spiro*heptadiene (III). After addition of the solution of the products in acetic acid (25 ml.) to a mixture of hydrogen peroxide (20 g.), concentrated sulphuric acid (0·5 ml.), and water (20 ml.), the resultant suspension was stirred at room temperature for 18 hr. during which the flocculent white precipitate dissolved. Evaporation *in vacuo* left a mixture of white crystals and colourless oil, which was separated into a neutral and an acidic (hydrogen carbonate-soluble) fraction. The former, a colourless non-ketonic oil (125 mg.), was not further investigated. The acidified hydrogen carbonate solution was extracted continuously with ether (24 hr.), yielding the acidic fraction (after drying and evaporation of the ether solution) as a mixture of crystals and oil (2 g.) which were separated by filtration. The acidic oil liberated iodine from potassium iodide and reacted violently with aniline, but could not be identified. The crystals were dried on porous plate and recrystallised from ether–ligroin (b. p. 40—60°) yielding *cyclo*pentane-1 : 1-dicarboxylic acid (0·31 g.; 10%),m. p. 185° (decomp.); mixed m. p. with authentic specimen (m. p. 189°) 187°. The infrared spectra of the two samples were identical.

*Oxidation of the Spiran* (IV) *with Potassium Permanganate*.—Finely ground potassium permanganate (12·5 g.) was added in small portions during 1 hr. to a vigorously stirred solution of the *spiro*nonadiene (IV) (1·2 g.) and sodium hydrogen carbonate (0·5 g.) in acetone (50 ml.) and the mixture was stirred overnight, then acidified with dilute sulphuric acid; sulphur dioxide was then passed in until a clear solution was obtained, and this was extracted continuously with ether for 24 hr. The resultant ether solution was extracted with sodium hydrogen carbonate solution, leaving a neutral oil (0·28 g.) in the organic layer. Acidification of the aqueous layer and re-extraction into ether followed by evaporation afforded oily crystals which were dissolved in benzene and precipitated by addition of ligroin, leaving a colourless oil (0·15 g.) in the mother liquors. Recrystallisation of the precipitate from chloroform–ligroin (b. p. 40—60°) afforded *cyclo*pentane-1 : 1-dicarboxylic acid (0·485 g.), m. p. 186° (decomp.), undepressed on admixture with an authentic specimen.

*Pyrolysis of the Spiran* (IV).—The *spiro*nonadiene (IV) (4 g.) was heated in a sealed tube at 130° for 24 hr. and the resulting yellow liquid was purified by passing its ligroin solution through a column of alumina. Evaporation of the solvent under reduced pressure left a colourless liquid (3·65 g.) which did not react with maleic anhydride, had an apparent molecular weight of 166, 169 (cryoscopic in benzene), and had only extremely weak maxima at 221 and 260 mμ [the latter being less than 2% of the intensity of the maximum at 256 mμ of the starting material (IV)]. Distillation of a portion of this material yielded a small fraction (0·28 g.), b. p. 100—105° (bath temp.)/19 mm. (Found: *M*, 119·5. Calc. for $C_9H_{12}$: *M*, 120·2), which like the crude product, failed to react with maleic anhydride. The remainder (1·65 g.) distilled from a bath at 110—120°/0·01 mm. and had the molecular weight calculated for a dimer (Found: 230, 234). This fraction was transparent in the ultraviolet region between 205 and 300 mμ.

*Reaction of the Spiran* (III) *with Iron Pentacarbonyl*.—The *spiro*heptadiene (III) (13 g.) and iron pentacarbonyl (28 g.) were heated under carbon dioxide in an autoclave at 140° for 36 hr. Extraction of the product with a small volume of acetone left a purple chloroform-soluble tar. The acetone solution was evaporated under reduced pressure to remove solvent and unchanged iron pentacarbonyl. The residual red oil was dissolved in the minimum amount of benzene and chromatographed on alumina (see preceding paper). The main purple band was eluted with benzene–ligroin (3 : 2), which, on evaporation, yielded purple crystals [216 mg.; 1·6% based on $Fe(CO)_5$]. Recrystallisation from ligroin afforded *bisethyl*cyclo*pentadienyldi-iron tetracarbonyl*, m. p. 61—62° (decomp.; vac.) (Found: C, 52·9, 53·1; H, 4·6, 4·7. $C_{18}H_{18}O_4Fe_2$ requires C, 52·7; H, 4·4%).

*Bistetrahydroindenyldi-iron Tetracarbonyl* (VII).—(*a*) *From the spiran* (IV). The *spiro*nonadiene (IV) (8 g.) and iron pentacarbonyl (12 g.) were heated under carbon dioxide in an autoclave at 130° for 25 hr., yielding a purple oil which was dissolved in the minimum amount of benzene and chromatographed on alumina (see preceding paper). The main purple band, eluted from the column with benzene–ligroin (3 : 2), gave, after evaporation of the solvent and addition of ligroin (b. p. 40—60°), purple crystals (6 g.; 39% based on *spiro*nonadiene), leaving an oil (3 g.) in the mother liquors. Recrystallisation of the solid product from ligroin (b. p. 60—80°) afforded *bistetrahydroindenyldi-iron tetracarbonyl* (VII), m. p. 148° (decomp., vac.) (Found: C, 57·2, 57·4; H, 4·9, 4·9. $C_{22}H_{22}O_4Fe$ requires C, 57·2; H, 4·8%). Infrared max. in the carbonyl stretching region at approx. 1951 and 1754 cm.$^{-1}$ (KBr disc).

This tetracarbonyl (VII) was recovered unchanged after its methanol solution had been stirred with hydrogen in the presence of Adams catalyst. A sample of (VII) (0·5 g.) was heated for a few minutes over a free flame and yielded an orange oil which was purified by chromatography on alumina and distillation at 130° (bath temp.)/0·05 mm. This oil was identified as bistetrahydroindenyliron by comparison of its infrared spectrum with that of an authentic specimen prepared by the method of Fischer and Seus.[4]

(*b*) ***From di-indenyldi-iron tetracarbonyl*** (VIII). To a solution of the tetracarbonyl (VIII) (0·1 g.) in ethanol (25 ml.), Adams catalyst (150 mg.) was added and the mixture was stirred under hydrogen until its uptake ceased (50 ml. at 743 mm. and 19°). Filtration and evaporation to small bulk yielded bistetrahydroindenyldi-iron tetracarbonyl, identical in appearance, m. p., mixed m. p., and infrared spectrum with the above sample.

***Di-indenyldi-iron Tetracarbonyl*** (VIII).—Freshly distilled indene (12 g.) and iron pentacarbonyl (20 g.) were heated together under carbon dioxide in an autoclave at 130° for 24 hr. The crystalline product, separated by filtration from an intractable red oil (6·2 g.), was purified by recrystallisation from chloroform–ligroin (b. p. 40—60°), yielding brownish-purple crystals of *di-indenyldi-iron tetracarbonyl* (VIII) (4·6 g.), m. p. 198° (decomp., vac.) (Found: C, 57·9, 57·6; H, 3·6, 3·5. $C_{22}H_{14}O_4Fe_2$ requires C, 58·2; H, 3·1%). Infrared max. in the carbonyl stretching region at approx. 1951 and 1790 cm.$^{-1}$ (as KBr disc).

The authors thank the University of Sheffield for the award of a Henry Ellison Fellowship (to B. F. H.).

THE UNIVERSITY, SHEFFIELD, 10. [*Received, July 19th,* 1957.]

---

## 127. *Ferrocene Derivatives. Part V.* Ferrocenealdehyde.*

By G. D. BROADHEAD, J. M. OSGERBY, and P. L. PAUSON.

Ferrocene is much more reactive towards Friedel–Crafts acylation than either benzene or anisole. The first acyl substituent deactivates even the unsubstituted ring. The high reactivity of ferrocene is utilised in its conversion into its mono-aldehyde by the *N*-methylformanilide method. This aldehyde shows the typical properties of an aromatic aldehyde; it undergoes the Cannizzaro reaction, has been converted *via* its oxime into ferrocenyl cyanide, and has also been condensed with malonic acid, with α-picoline methiodide, and, in a mixed benzoin condensation, with benzaldehyde. An alternative preparation of the aldehyde is also described.

IN our detailed study of the Friedel–Crafts acetylation of ferrocene we sought at least a semiquantitative comparison of the reactivity of ferrocene with that of benzene or its simple derivatives from competitive experiments. Although this quantitative information was not obtained, the results gave us a better understanding of the reactivity of ferrocene and are therefore briefly reported now.

Woodward and his collaborators [1] were the first to prepare diacetylferrocene by this reaction. They had also established [2] that the monoacetyl derivative, whose preparation was subsequently reported from several other laboratories,[3,4] could be obtained efficiently by using a methylene chloride or chloroform solution of the aluminium chloride–acetyl chloride complex. We found that use of equimolecular proportions of ferrocene and of this reagent yields only traces of the disubstitution product. It follows that, under essentially homogeneous reaction conditions, the first substitution step must be very much faster than the second. We believe that this result can only be understood on the basis

* Part IV, preceding paper.

[1] Woodward, Rosenblum, and Whiting, *J. Amer. Chem. Soc.*, 1952, **74**, 2125.
[2] Woodward *et al.*, personal communication.
[3] Nesmeyanov, Perevalova, Golovnya, and Nesmeyanova, *Doklady Akad. Nauk S.S.S.R.*, 1954, **97**, 459.
[4] Weinmayr, *J. Amer. Chem. Soc.*, 1955, **77**, 3009.

of a very marked deactivating effect exerted by the first substituent towards substitution in the second (unsubstituted) ring, as well as, of course, in the same ring. That acylation with milder Friedel–Crafts catalysts, *e.g.*, stannic chloride,[3] hydrogen fluoride,[4] phosphoric acid,[4a] and, in the present work (recently confirmed by Hauser [5]), boron trifluoride, stops, apparently completely, at the monosubstitution stage confirms this. Similarly other reactions which require relatively reactive aromatic substrates, *e.g.*, aminomethylation [6,7,8] and the formylation reported below, lead to exclusive monosubstitution of ferrocene.

Aluminium chloride-catalysed acylation of ferrocene readily leads to disubstitution [1] and this occurs not only with a sufficient excess of acetyl chloride–aluminium chloride complex, but becomes the main result even when excess of aluminium chloride is employed in a reaction in which ferrocene is present in excess over acetyl chloride. This is probably the result of the heterogeneous nature of the reaction under these conditions. (A complex between acetylated ferrocene and aluminium chloride separates rapidly from the chloroform solution, and if this layer may be assumed to extract most of the unchanged acetyl chloride–aluminium chloride complex from the supernatant solution of ferrocene, the above observation is readily accounted for.)

Competitive experiments with benzene and anisole were attempted by using the preformed 1 : 1 acetyl chloride : aluminium chloride complex. Acetylferrocene was the only ketonic product formed in all such experiments and no acetophenone or methoxyacetophenone was detected, although up to 10 : 1 molar ratios of anisole : ferrocene were employed. Even a competitive experiment with phenol afforded acetylferrocene as the only ketonic product, but no attempt was made in this case to find phenyl acetate. These observations clearly indicate that ferrocene is substantially more reactive than anisole and probably at least comparable with phenol. We sought confirmation of this deduction by attempting to couple ferrocene with diazonium salts under conditions applicable to anisole,[9] and were thus led to discover the remarkably facile arylation of ferrocene described in Part II.[10] Independent confirmation has more recently been provided by the demonstation that ferrocene undergoes a Mannich-type condensation with formaldehyde and dimethylamine.[6,7]

Another consequence was the realisation that the mild methods used to prepare aldehydes from highly reactive aromatic compounds might be applicable to ferrocene. This was substantiated when we treated ferrocene with a mixture of *N*-formylmethylaniline and phosphorus oxychloride.[11,12] The same method has been employed independently by Rosenblum.[13] *

We have also obtained ferrocenecarboxyaldehyde (I) from dimethylaminomethylferrocene methiodide [6,7,8] by the Sommelet reaction, using the procedure introduced by Hewett.[14] Lindsay and Hauser [7] recently used the same starting material for a two-step preparation of the aldehyde (I). This compound yields the usual carbonyl derivatives, but is not very reactive. For instance, it is not extracted from ethereal solution by saturated aqueous bisulphite, although the solid reacts with this reagent. Ethylene glycol converts the aldehyde (I) into the cyclic acetal (II), but the extreme ease with which

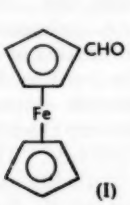
* After this paper was submitted a further preparation of the aldehyde by this method, but under less favourable experimental conditions, was described by Graham *et al.*,[4a] who also report alternative procedures for its conversion into ferrocenylmethanol and ferrocenyl cyanide.

[4a] Graham, Lindsey, Parshall, Peterson, and Whitman, *J. Amer. Chem. Soc.*, 1957, **79**, 3416.
[5] Hauser and Lindsay, *J. Org. Chem.*, 1957, **22**, 482.
[6] *Idem, ibid.*, 1956, **21**, 382.
[7] Lindsay and Hauser, *ibid.*, 1957, **22**, 355.
[8] Part VI, following paper.
[9] Meyer and Lenhardt, *Annalen*, 1913, **398**, 66; Meyer, Irschick, and Schlösser, *Ber.*, 1914, **47**, 1741.
[10] Part II, *J.*, 1955, 367.
[11] Broadhead, Thesis, Sheffield, July 1956.
[12] Broadhead, Osgerby, and Pauson, *Chem. and Ind.*, 1957, 209.
[13] Rosenblum, *ibid.*, 1957, 72.
[14] Hewett, *J.*, 1940, 293; cf. Badger, *J.*, 1941, 535; Angyal, Morris, Tetaz, and Wilson, *J.*, 1950, 2141.

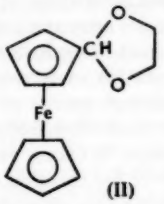
XUM

this acetal hydrolyses back to the aldehyde (I) precluded the use of this protective device for further substitutions designed to yield, *e.g.*, the dialdehydes.

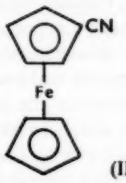
The oxime of the aldehyde has been isolated in both *syn*- and *anti*-forms and these have both been converted into the corresponding nitrile (III). This dehydration resulted, in



(I)

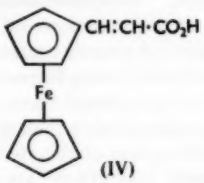


(II)

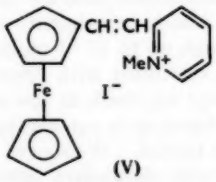


(III)

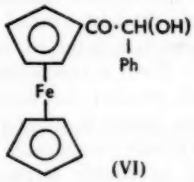
place of Beckmann rearrangement, when the oxime was treated with phosphorus pentachloride, and again when an isomerisation to the amide was attempted by the Raney nickel method.[15] Conversion into the nitrile proceeded more smoothly with acetic anhydride, but the most efficient method found for the dehydration of either stereoisomer



(IV)



(V)



(VI)

of the oxime was the use of di*cyclo*hexylcarbodi-imide.† Ferrocenyl cyanide has also been obtained in minute yield by direct Friedel–Crafts reaction of ferrocene with cyanogen bromide.

The aldehyde (I) is stable to dilute alkalis, and the Cannizzaro reaction proceeded only under rather vigorous conditions. An attempted "crossed Cannizzaro reaction" with formaldehyde did not improve the yield of ferrocenylmethanol. The latter was best obtained by reduction of the aldehyde with sodium borohydride. The aldehyde (I) condenses smoothly with typical compounds containing reactive methylene groups, *e.g.*, with malonic acid yielding ferrocenylacrylic acid (IV), with hippuric acid,[8] and with 1:2-dimethylpyridinium iodide giving the purple stilbazole (V). The aldehyde was, however, recovered unchanged from an attempted benzoin condensation, although, when a mixture

TABLE 1. *Infrared carbonyl stretching frequencies* (*in cm.*$^{-1}$; $CHCl_3$ *solution*).

| | R·CHO | R·CO·$CH_3$ | R·CO·CH(OH)·$C_6H_5$ [a] |
|---|---|---|---|
| R = $C_6H_5$ ..... | 1703 [b] | 1683 [b] | 1681 |
| R = $C_{10}H_9Fe$ ..... | 1676, 1666 [c] | 1672 [d] | 1668, 1648 |

[a] As KBr disc. [b] Hartwell *et al.*[16] give 1705 and 1687 cm.$^{-1}$ for liquid benzaldehyde and acetophenone, respectively. [c] The exact figures are doubtful (within perhaps 5 cm.$^{-1}$) owing to incomplete resolution of this doublet, but the average (1671) should be comparable with the other figures quoted. Failure to recognise this band as a doublet undoubtedly accounts for the discrepancy between the values previously recorded.[12, 13] The values now observed for KBr discs, both of this compound and of acetylferrocene, are within experimental error (±2 cm.$^{-1}$) of those observed in solution. [d] Rosenblum [17] gives 1675 cm.$^{-1}$.

with an equimolecular amount of benzaldehyde was treated under the same conditions, the acyloin (VI) was formed in moderate yield. That this product has the structure (VI)

† The use of this reagent was suggested to us by Dr. D. T. Elmore. It does not appear to have been employed previously for the dehydration of oximes.

[15] Paul, *Bull. Soc. chim. France*, 1937, **4**, 1115.
[16] Hartwell, Richards, and Thompson, *J.*, 1948, 1436.
[17] Rosenblum, Thesis, Harvard, 1953.

rather than the tautomeric benzoyl-ferrocenylmethanol structure follows from a comparison of the carbonyl stretching frequencies listed in Table 1. In common with the other two ferrocene derivatives, the product (VI) absorbs at a lower frequency than the corresponding benzene derivatives. This difference is particularly large in the case of the two aldehydes—a fact which emphasises the strong polarisation of the carbonyl group in ferrocenecarboxyaldehyde. This is also indicated by its basicity—the aldehyde (I) can be extracted from organic solvents with aqueous hydrochloric acid.

## Experimental

"Alumina" used for chromatography refers to Spence's "Type H; 100/200's mesh" which had been partially deactivated by exposure to air for 6 hr.

*Acetylation of Ferrocene and Acetylferrocene.*—The reagent used in all experiments was prepared by dissolving a known weight of acetyl chloride in dry alcohol-free chloroform and allowing this solution to stand in contact with excess of aluminium chloride for 2 hr. Addition of water to such solutions followed by gravimetric estimation of aluminium by the oxine method indicated that 90% of the aluminium chloride required to form a 1 : 1 AcCl : $AlCl_3$ complex had been dissolved. This reagent was added during 15—20 min. to a stirred solution of ferrocene in chloroform, under nitrogen at 0° (Table 2). [Results (not listed) obtained at 20° were similar, but yields decreased with time owing to the formation of tars.] After stirring for the time specified, ice was added to the reaction mixture together with sufficient titanous sulphate solution to reduce any ferricinium salt present. The organic layer was separated, dried, and evaporated, and the residue chromatographed on alumina with benzene as solvent.

Table 2.

| Ferrocene (moles) | AcCl (moles) | Time [a] (hr.) | Ferrocene recovered (%) | Acetylferrocene [b] (%) | Diacetylferrocene [b] (%) | Total ferrocene accounted for (%) |
|---|---|---|---|---|---|---|
| 0·013 | 0·013 | 0·5 | 53 | 47 [c] (89) | tr.[d] | 95 |
| 0·011 | 0·011 | 0·5 | 50 | 47 [c] (86) | tr.[d] | 92 |
| 0·018 | 0·018 | 1·5 | 44 | 54 [c] (86) | tr.[d] | 92 |
| 0·016 | 0·05 | 1 | 0 | 3 [e] | 73 [e] | 76 |
| 0·018 | 0·09 | 1·5 | 6 | 15 [e] (17) | 71 [e] (76) | 92 |
| 0·02 | 0·018 [f] | 1·5 | 56 | 9·7 [c] (20)<br>8·8 [e] | 54 [c] (56)<br>24·5 [e] | 89 |
| 0·016 | 0·016 [g] | 5 | 55 | 13 [e] (26) | 19 [e] (38) | 85 |

[a] Includes time of addition. [b] Yields in parentheses are corrected for recovered ferrocene. [c] Based on AcCl–$AlCl_3$ complex assuming 90% formation from AcCl. [d] Nil or trace (less than 0·5%). [e] Based on ferrocene. [f] Additional $AlCl_3$ (2·7 g.; 0·02 mole) added to the ferrocene before addition of AcCl–$AlCl_3$ complex. [g] $AlCl_3$ (6 g.) added as in (*f*).

Similar acetylations of acetylferrocene were found to require the addition of solid aluminium chloride and then gave 85% yields of diacetylferrocene and 10% of unchanged monoacetyl derivative after 2 hr. (equimolecular amounts of acetylferrocene and acetyl chloride being used). Without free aluminium chloride only 1% of diacetylferrocene was formed, probably owing to preferential complex formation by the acetylferrocene which therefore abstracted the aluminium chloride from the 1 : 1 acetyl chloride–aluminium chloride complex added to it.

*Preparation of Acetylferrocene by Use of Acetic Anhydride–Boron Trifluoride.*—Ferrocene (3 g.; 0·016 mole) and acetic anhydride (1·64 g.; 0·015 mole) were dissolved in dry chloroform and cooled to 0°. Dry boron trifluoride was passed in for 2 hr., and the solution then left for a further 4 hr. at 0°. After working up as above, ferrocene (0·36 g.; 13%) was recovered and acetylferrocene (2·36 g.; 73% based on unrecovered ferrocene) was obtained.

*Attempted Competitive Acetylations of Ferrocene and Benzene, Anisole, or Phenol.*—These were carried out in the same manner as the experiments listed in Table 2. The reactants were employed in the following proportions (moles), and the yields (based on the complex) were as shown:

| | Ferrocene | AcCl | Third component | Yield (%) |
|---|---|---|---|---|
| (*a*) | 0·02 | 0·014 | Benzene, 0·02 | 50 |
| (*b*) | 0·018 | 0·012 | Anisole, 0·018 | 35 |
| (*c*) | 0·018 | 0·016 | ,, 0·18 | 47 |
| (*d*) | 0·016 | 0·016 | Phenol, 0·016 | 9 |

XUM

In experiment (*d*) 91% of the ferrocene was recovered unchanged. No other ketonic products were detected in any of these experiments although it had been demonstrated separately that both acetophenone and *p*-methoxyacetophenone are readily separated from acetylferrocene by chromatography and that both are almost quantitatively precipitated by 2 : 4-dinitrophenylhydrazine under the conditions used.

*Ferrocenecarboxyaldehyde* (I).—(a) N-*Methylformanilide method.* *N*-Methylformanilide (4·4 g.; 0·032 mole) and phosphorus oxychloride (5 g.; 0·032 mole) were mixed and left at room temperature for 1 hr. Ferrocene (2·99 g.; 0·016 mole) was then added in small portions with vigorous shaking during approx. 30 min., the mixture being kept cool throughout. It was then left in a stoppered flask for 72 hr. After addition of ice-water, the mixture was left for some hours to ensure complete decomposition of the complex. The product was extracted with chloroform, and the solution dried ($Na_2SO_4$) and evaporated. A benzene solution of the residue was chromatographed on alumina to separate the product from unchanged ferrocene (0·125 g.; 4·2%) and *N*-methylformanilide. The main red band was eluted with benzene, evaporated, and crystallised from 25% aqueous ethanol to yield *ferrocenecarboxyaldehyde* (I) (2·56 g.; 77·6%), m. p. 119—120°, raised by further crystallisation from the same solvent or from light petroleum (b. p. 40—60°) to 121° (Found: C, 61·4; H, 4·9. $C_{11}H_{10}OFe$ requires C, 61·7; H, 4·7%). This aldehyde is volatile in steam and sublimes at 70°/0·01 mm. Ultraviolet max. in methanol: 226, 271, 344, and 461 mμ (log ε 4·23, 3·88, 3·17, and 2·78).

(b) *Sommelet method.* To ferrocenylmethyltrimethylammonium iodide [5] (4·5 g.; 0·012 mole) dissolved in glacial acetic acid (22 ml.), hexamethylenetetramine (5·7 g.; 0·04 mole) was added, and the mixture boiled for 1 min. The solution was poured into water and extracted with benzene. Evaporation under reduced pressure and recrystallisation from aqueous ethanol yielded the above aldehyde (0·92 g.; 37%).

*Ferrocenecarboxyaldoxime.*—This compound was isolated in two distinct forms, depending on the method of preparation. Recrystallisation of each form appeared to cause partial conversion into the other, and, as mixtures showed intermediate m. p.s it remains doubtful whether either form has been obtained quite pure. The " α "-form is tentatively assigned the *syn*- and the " β "-form the *anti*-configuration by analogy to the benzaldoximes. In each case the *syn*-isomer has the lower m. p., is more acidic, and is formed under basic reaction conditions, whereas the *anti*-isomer is formed in acidic medium. The " α "-form was produced essentially under the conditions described by Lindsay and Hauser [7] and had the same properties. A sample of the same m. p. (90—92°) was obtained in a preparation carried out as described below, under (*a*), for the " β "-isomer, but in which the product was chromatographed on alumina using benzene as solvent to remove a trace of unchanged aldehyde, and, after removal of the latter, eluted with ethanol. This sample was repeatedly recrystallised from ligroin, and a sample which then had m. p. 96—99° was analysed (Found: C, 57·9; H, 5·0; N, 5·9. Calc. for $C_{11}H_{11}ONFe$: C, 57·7; H, 4·8; N, 6·1%). This isomer dissolves readily in 2N-sodium hydroxide. To recover the oxime from such solutions it is necessary to acidify them carefully at low temperature or, preferably, with solid carbon dioxide, to avoid partial hydrolysis to the free aldehyde.

The " β "-isomer has been obtained by the following two procedures: (*a*) To hydroxylamine hydrochloride (0·7 g.) and anhydrous sodium acetate (1 g.) dissolved in water (4 ml.) were added ferrocenecarboxyaldehyde (I) (1 g.) and enough ethanol (*ca.* 6 ml.) to produce a homogeneous solution on warming. The mixture was refluxed for 2—3 hr., cooled, and extracted with ether, and the ether solution washed repeatedly with 2N-sodium hydroxide. The aqueous layer on acidification yielded only a small amount (less than 0·1 g.) of oxime of very indefinite m. p. The ether layer was dried and evaporated, and the residue crystallised once from benzene, yielding " β "-*ferrocenecarboxyaldoxime* (0·5 g.) as orange prisms, m. p. 155—157°. Four more crystallisations from benzene gradually lowered this m. p. to 145—146° (Found: C, 57·7; H, 4·7; N, 6·25%).

(*b*) A solution of the aldehyde (I) (1·5 g.) and hydroxylamine hydrochloride (0·7 g.) in ethanol (10 ml.) was refluxed under nitrogen for 2 hr. After cooling the black oxime hydrochloride (1·34 g.; 70%) was filtered off. This was suspended in ether, and the free oxime liberated by shaking with sodium carbonate solution. Evaporation of the dried ether solution and crystallisation from benzene afforded the β-oxime, m. p. 150—152°. The product, m. p. 138—140°, described by Rosenblum [13] is presumably predominantly this β-form of the oxime. Graham *et al.*[42] give m. p. 133—135° for this oxime.

*Ferrocenyl Cyanide* (III).—(a) *Carbodi-imide method.* The β-oxime (0·15 g.) and dicyclohexylcarbodi-imide (0·17 g.) were refluxed in benzene (10 ml.) for 6 hr. On cooling, dicyclohexylurea (0·12 g.) was filtered off. The benzene solution was then thoroughly extracted with dilute sodium hydroxide, which removed unchanged oxime (15 mg.; 10%). Evaporation of the benzene and crystallisation of the residue from light petroleum afforded the nitrile (97 mg.; 78% based on unrecovered oxime), identical in m. p. and mixed m. p. with the product described under (b). Under identical conditions the α-oxime yielded 70 mg. (50%) of nitrile and 14 mg. (9%) of unchanged oxime.

(b) *Acetic anhydride method.* The oxime (mixed α- and β-) (1 g.) and acetic anhydride (10 ml.) were gently warmed together for 20 min. and then refluxed for a further 20 min. The solution was poured into water (30 ml.) and extracted with chloroform, and the extract washed until neutral, dried, and evaporated. The residue was purified by chromatography on alumina followed by crystallisation from light petroleum (b. p. 40—60°), *ferrocenyl cyanide* (III) forming golden-yellow plates, m. p. 107—108° (Found: C, 62·7; H, 4·5. $C_{11}H_9NFe$ requires C, 62·6; H, 4·3%). Infrared max. in the carbon–nitrogen triple-bond stretching region at 2242 cm.$^{-1}$ (KBr disc).

(c) *Phosphorus pentachloride method.* The oxime (mixed isomers) (1 g.), dissolved in anhydrous ether (25 ml.), was treated with phosphorus pentachloride (1·5 g.). After the initially vigorous reaction had subsided, the mixture was shaken for 2 hr. Chloroform was then added, and ferrocenyl cyanide (0·2 g.; 25%) isolated as above, its identity being established by mixed m. p. and comparison of infrared spectra with the product described under (b).

(d) *By use of Raney nickel.* To the oxime (mixed isomers) (1·8 g.) dissolved in absolute alcohol (40 ml.), a suspension of Raney nickel (approx. 2 g.) in the same solvent was added, and the whole shaken for 48 hr. After addition of water and working up as above, the nitrile (0·1 g.; 6%) was obtained together with unchanged oxime (0·6 g.; 30%) and a trace of free aldehyde (0·04 g.).

(e) *From ferrocene and cyanogen bromide.* To a mixture of ferrocene (6 g.; 0·032 mole), anhydrous aluminium chloride (8·4 g.; 0·06 mole), and carbon disulphide, under nitrogen, a solution of cyanogen bromide (4·24 g.; 0·04 mole) in the same solvent was slowly added at 0°. The mixture was left for 4 hr. and then refluxed for 1 hr. After addition of ice and titanous sulphate solution, the products were worked up as above, yielding unchanged ferrocene (4 g.; 66%) followed on the chromatogram by a trace of ferrocenyl cyanide, identified by its infrared spectrum. All attempts to improve the yield, *e.g.*, by change of solvent, failed.

*2-Ferrocenyl-1 : 3-dioxolan* (II).—The aldehyde (I) (2 g.; 0·009 mole) was added to a mixture of benzene, ethylene glycol (1 ml.; 0·018 mole), and a trace of toluene-*p*-sulphonic acid. This mixture was allowed to reflux overnight through a Soxhlet apparatus filled with anhydrous calcium sulphate. Evaporation of the solution and chromatography of the residue on alumina, using *cyclo*hexane as solvent, separated the *cyclic acetal* (II) (2 g.; 94%) from a trace of unchanged aldehyde (0·12 g.; 6%). The acetal crystallised from light petroleum (b. p. 40—60°) as golden-yellow needles, m. p. 81—82° (Found: C, 60·5; H, 5·8. $C_{13}H_{14}O_2Fe$ requires C, 60·5; H, 5·5%).

*Ferrocenylmethanol.*—(a) *By borohydride reduction.* Addition of sodium borohydride (0·061 g.) to a solution of ferrocenecarboxyaldehyde (I) (0·26 g.) in methanol (5 ml.) caused immediate reduction as indicated by the change in colour from red to yellow. Evaporation of the solvent and recrystallisation from water afforded *ferrocenylmethanol* (hydroxymethylferrocene) (0·216 g.; 85%), m. p. 76° (Found: C, 61·4; H, 5·4. $C_{11}H_{12}OFe$ requires C, 61·2; H, 5·6%).

(b) *By Cannizzaro reaction.* The aldehyde (I) (0·5 g.) was refluxed for 3 hr. with 50% alcoholic potassium hydroxide (10 ml.). After cooling, the mixture was diluted with water and extracted with ether. Evaporation of the ether layer afforded ferrocenylmethanol (0·12 g.; 47%), m. p. (and mixed m. p.) 76°. Acidification of the alkaline layer, extraction with ether, and evaporation of the extract yielded ferrocenecarboxylic acid (0·025 g.; 10%), m. p. 210° (decomp.) undepressed by an authentic specimen.

(c) *By attempted crossed Cannizzaro reaction.* A mixture of ferrocenecarboxyaldehyde (I) (1 g.) and aqueous formaldehyde (1 ml. of 40%) dissolved in methanol (10 ml.) was heated to 65° and treated with potassium hydroxide (2·66 g. dissolved in 2 ml. of water). After refluxing for 3 hr. and working up as above, the neutral product was chromatographed on alumina with benzene as solvent. In this way ferrocenylmethanol (0·045 g.; 9%) was separated from unchanged aldehyde (0·5 g.).

XUM

β-*Ferrocenylacrylic Acid* (IV).—The aldehyde (I) (0·5 g.), malonic acid (0·5 g.), and piperidine (10 drops; *ca.* 0·1 ml.) were dissolved in pyridine (12 ml.) and heated under nitrogen on a boiling-water bath for 2 hr. The cooled solution was diluted with water and extracted with chloroform. The chloroform extract was washed with dilute hydrochloric acid and water, and then extracted with 2N-sodium hydroxide. Acidification of the aqueous layer precipitated the brick-red β-*ferrocenylacrylic acid* (IV) (0·4 g.; 68%). Recrystallisation from benzene afforded deep red prisms, m. p. 186—187° (decomp.; efferv.) (Found: C, 61·5, 61·6, 61·7; H, 5·1, 5·2, 5·0; O, 12·4, 12·4. $C_{13}H_{12}O_2Fe$ requires C, 61·0; H, 4·7; O, 12·5%).

1-*Ferrocenyl*-2-(2-*pyridyl*)*ethylene Methiodide* (V).—The aldehyde (I) (0·3 g.), 1 : 2-dimethylpyridinium iodide (0·3 g.) and piperidine (1 ml.) were dissolved in methanol (20 ml.) and refluxed for 3 hr. under nitrogen. On evaporation of the resultant solution to small bulk, the *stilbazole* (V) partly crystallised as deep purple prisms (Found: C, 49·7; H, 4·5; N, 2·9. $C_{18}H_{18}NIFe$ requires C, 50·2; H, 4·2; N, 3·25%). This compound is soluble in polar organic solvents and in water and insoluble in ether or hydrocarbon solvents, but no satisfactory method of recrystallisation has been found.

*Mandeloylferrocene* (VI).—A mixture of the aldehyde (I) (1·07 g.; 0·005 mole), benzaldehyde (0·53 g.; 0·005 mole), ethanol (15 ml.), and aqueous potassium cyanide (0·5 g. in 1 ml. water) was refluxed for 1·5 hr. After dilution with water and refrigeration for 2 hr. the product was filtered off and recrystallised from aqueous alcohol. The *acyloin* (VI) formed fine pink needles (0·37 g.; 25%), m. p. 148—149° (Found: C, 67·5; H, 5·1. $C_{18}H_{16}O_2Fe$ requires C, 67·5; H, 5·0%).

The authors thank the Minnesota Mining and Manufacturing Company for a grant (to J. M. O.), the University of Sheffield for a Henry Ellison Fellowship (to G. D. B.), and E.I. du Pont de Nemours and Company for gifts of ferrocene.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, July 19th,* 1957.]

---

## 128. *Ferrocene Derivatives. Part VI.*[1] DL-*Ferrocenylalanine.*

By J. M. OSGERBY and P. L. PAUSON.

Syntheses of DL-ferrocenylalanine from ferrocenecarboxyaldehyde by the azlactone method, and, more efficiently, from (ferrocenylmethyl)trimethylammonium iodide *via* (ferrocenylmethyl)formamidomalonic ester are described. The latter starting material has also been converted into ferrocenyl-acetic and -propionic acid.

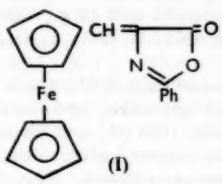
THE availability of ferrocenecarboxyaldehyde [1] suggested several obvious routes to amino-acids containing the ferrocene nucleus. The biological properties of ferrocenylalanine appeared to be of potential interest and its preparation by the azlactone method was therefore chosen for initial study.

Condensation with hippuric acid converted the aldehyde smoothly into the desired azlactone (I) and this was readily hydrolysed to α-benzamido-β-ferrocenylacrylic acid. Reduction with sodium and ethanol converted both this acid and its azlactone precursor (I) into β-ferrocenyl-α-*cyclo*hexylformamidopropionic acid (II). This acyl derivative (II) of ferrocenylalanine (III) was unaffected by carboxypeptidase and gave only a trace of ninhydrin-positive material on alkaline hydrolysis. Acid hydrolysis afforded the desired amino-acid (III) but only in minute yield. Numerous variations of the conditions failed to improve this or to reduce the extensive decomposition to tar which accompanied hydrolysis. As amides of formic acid are hydrolysable under much milder conditions, attention was turned to the formamidomalonic ester method. This ester is usually condensed in the form of its sodio-derivative with a reactive halide. The necessary ferrocenylmethyl chloride or bromide was, however, then unknown and, although Dr. K.

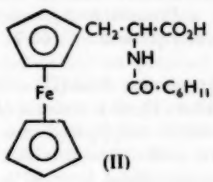
[1] Part V, preceding paper.

Schlögl [2] kindly informed us that he was attempting its preparation for the same purpose, we decided to explore the use of the much more readily available quaternary salt (IV).

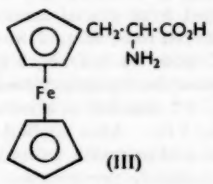
The preparation of (ferrocenylmethyl)trimethylammonium iodide (IV) from ferrocene by the action of methylenebisdimethylamine in glacial acetic acid [3] was improved by the addition of phosphoric acid to the reaction mixture. Under these conditions the salt (IV) was isolated in quantitative yield without purification of the intermediate tertiary



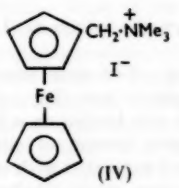
(I)



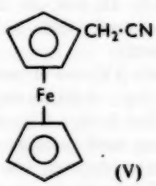
(II)



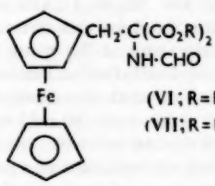
(III)



(IV)



(V)



(VI; R = Et)
(VII; R = H)

amine. The same conditions have been applied to the preparation of *N*-(ferrocenylmethyl)piperidine in 70% yield.

To demonstrate the reactivity of the salt (IV) in condensations of the type required for its conversion into (ferrocenylmethyl)formamidomalonic ester (VI) its reactions with potassium cyanide and with diethyl sodiomalonate were first studied. Cyanide reacts smoothly to yield ferrocenylacetonitrile (V) which has been identified by hydrolysis to the corresponding acid. We had already obtained the latter by the Willgerodt reaction * on acetylferrocene followed by alkaline hydrolysis of the resultant thiomorpholide.

Diethyl malonate reacted with (IV) in the presence of sodium ethoxide to give an oily ester which was hydrolysed and decarboxylated to ferrocenylpropionic acid, also obtained by catalytic hydrogenation of ferrocenylacrylic acid [1] and identical with an authentic specimen [5] kindly supplied by Dr. E. Csendes. Similar condensation of the quaternary ammonium salt (IV) with formamidomalonic ester afforded the desired product (VI). Hydrolysis of this by 5N-hydrochloric acid yields the amino-acid (III) directly. Alternatively, alkaline hydrolysis converts the ester (VI) into the corresponding free acid (VII) which is then further hydrolysed and decarboxylated to (III) by brief treatment with acid.

## Experimental

*Azlactone* (I).—Ferrocenecarboxyaldehyde (1 g.; 4·7 mmoles), hippuric acid (1 g.; 5·6 mmoles), and anhydrous sodium acetate (0·4 g.; 5 mmoles) were dissolved in acetic anhydride (4 ml.) by refluxing for 5 min. in a stream of nitrogen. The solution was then heated for 1·5 hr. on a steam-bath, cooled, diluted with methanol (6 ml.), and refrigerated overnight. Filtration followed by recrystallisation from benzene–ligroin (b. p. 60—80°) afforded the *azlactone* (I)

* The use of this method was briefly reported by one of us [4] and has recently been extended and mproved by Rinehart *et al.*[5] and by Graham *et al.*[5a]

[2] Schlögl, personal communication, and *Monatsh.*, 1957, **88**, 601.
[3] Hauser and Lindsay, *J. Org. Chem.*, 1956, **21**, 382; 1957, **22**, 355.
[4] Pauson, *Quart. Reviews*, 1955, **9**, 391.
[5] Rinehart, Curby, and Sokol, *J. Amer. Chem. Soc.*, 1957, **79**, 3420.
[5a] Graham, Lindsey, Parshall, Peterson, and Whitman, *ibid.*, p. 3416.

(0·964 g.; 58%) as deep purple crystals, m. p. 188° (Found: C, 66·5, 67·7, 67·4; H, 4·55, 4·3, 4·5; N, 3·8, 4·1. $C_{20}H_{15}O_2NFe$ requires C, 67·2; H, 4·2; N, 3·9%).

No crystalline azlactone could be obtained when acetylglycine was employed in place of hippuric acid.

*α-Benzamido-β-ferrocenylacrylic Acid.*—The above azlactone (I) (2 g.; 5·6 mmoles) was refluxed for 15 min. with a solution of sodium hydroxide (0·6 g.) in 50% aqueous ethanol (25 ml.). After cooling and acidifying with 2N-hydrochloric acid, the red precipitate was collected and recrystallised from glacial acetic acid. *α-Benzamido-β-ferrocenylacrylic acid* (2 g.; 95%) was obtained as red rods, m. p. 218—219° (vac.) (Found: C, 63·7; H, 4·65; N, 3·9. $C_{20}H_{17}O_3NFe$ requires C, 64·0; H, 4·5; N, 3·7%).

*β-Ferrocenyl-α-(cyclohexylformamido)propionic Acid* (II).—To a solution of the above acrylic acid (1 g.; 2·7 mmoles) in absolute ethanol (40 ml.), sodium (4 g.) was added, and the mixture refluxed for 1 hr. After cooling, the solution was poured into water (100 ml.) and filtered, and the filtrate acidified with 2N-hydrochloric acid. The product was collected after refrigeration, to ensure complete precipitation, and recrystallised from 50% aqueous ethanol. The *acid* (II) was obtained as orange-yellow plates, m. p. 222—223° (decomp.; vac.) (Found: C, 62·5; H, 6·5; N, 3·9. $C_{20}H_{23}O_3NFe$ requires C, 62·7; H, 6·6; N, 3·7%).

The same product was obtained in lower overall yield (38%) when the azlactone (I) (1 g.) was similarly reduced (by using 5·3 g. of sodium).

*(Ferrocenylmethyl)trimethylammonium Iodide* (IV).—Ferrocene (9 g.; 0·05 mole) was added to a mixture of methylenebisdimethylamine (8 g.; 0·08 mole), phosphoric acid (8 g.; *d* 1·75), and glacial acetic acid (80 ml.) in a three-necked flask. The mixture was heated on a boiling-water bath for 10 hr. with continuous stirring and passage of a slow stream of nitrogen. After cooling, the solution was poured into water (approx. 100 ml.) and extracted with ether to remove any trace of unchanged ferrocene. The aqueous layer was then made alkaline with sodium hydroxide and extracted with ether, and the extract dried and evaporated (finally *in vacuo*). The residue (dimethylaminomethylferrocene) was taken up in benzene and excess of methyl iodide was carefully added to precipitate the methiodide [3] as a yellow solid, m. p. 220° (decomp.).

*Piperidinomethylferrocene.*—Ferrocene (0·9 g.; 0·005 mole) was added to a mixture of methylenebispiperidine (1·8 g.; 0·01 mole), phosphoric acid (1 g.; *d* 1·75), and glacial acetic acid (10 ml.). The resulting solution was refluxed under nitrogen for 8 hr., cooled, diluted with an equal volume of water, and extracted with ether. Neutralisation of the aqueous layer precipitated *piperidinomethylferrocene* (0·72 g.), and a further quantity (0·22 g.) was extracted from the mother-liquors with ether. The product crystallised in yellow leaflets from aqueous ethanol and after further crystallisation from ligroin (b. p. 40—60°) had m. p. 84—85·5° (Found: C, 68·1; H, 7·25; N, 4·8. $C_{16}H_{21}NFe$ requires C, 67·9; H, 7·5; N, 4·95%).

*Ferrocenylacetonitrile* (V).—The quaternary salt (IV) (3·9 g.; 0·01 mole) was added to a solution of potassium cyanide (1·0 g.; 0·015 mole) in absolute ethanol (10 ml.), and the mixture refluxed for 2 hr. under nitrogen. After cooling, ether was added to precipitate unchanged quaternary salt (0·92 g.), and the mixture filtered. The filtrate was diluted with water, and the aqueous layer extracted with more ether. The combined ether extracts were dried and evaporated, and the residue crystallised from aqueous ethanol, giving yellow leaflets (0·83 g.; 48%), m. p. 81°. After further purification by chromatography on alumina and crystallisation from ligroin (b. p. 40—60°) *ferrocenylacetonitrile* had m. p. 85° (Found: C, 64·0; H, 5·2; N, 6·1. $C_{12}H_{11}NFe$ requires C, 64·0; H, 4·9; N, 6·2%).

*Ferrocenylacetic Acid.*—(a) *From the nitrile.* The nitrile (V) (0·105 g.) was refluxed with a solution of sodium hydroxide (1 g.) in a mixture of ethanol (9 ml.) and water (7 ml.) for 1·5 hr. The cooled solution was diluted with more water and extracted with ether, and the aqueous layer acidified with dilute hydrochloric acid. The precipitated *ferrocenylacetic acid* was extracted with ether and crystallised from *cyclo*hexane, from which it formed pale yellow platelets (0·07 g.; 60%) which shrank to a semisolid mass at *ca.* 140° and finally melted at 161° (vac.) (Found: C, 59·4; H, 5·5. $C_{12}H_{12}O_2Fe$ requires C, 59·05; H, 5·0%).

(b) *From acetylferrocene.* A mixture of acetylferrocene (1 g.), sulphur (0·2 g.), and morpholine (0·6 g.) was heated on a steam-bath for 1·5 hr. and then at 130° ± 10° for 1 hr. After cooling, extraction of the black mass with ligroin (b. p. 40—60°) yielded *ferrocenylacet-thiomorpholide*, m. p. 125—126°. Recrystallisation from ligroin (b. p. 60—80°) gave orange-yellow needles (0·2 g.), m. p. 127—128° (Found: C, 58·8; H, 6·0. $C_{16}H_{19}ONSFe$ requires

C, 58·4; H, 5·8%). Reduction of reaction time or temperature afforded mixtures containing much unchanged ketone.

The thiomorpholide (0·1 g.) was refluxed for 3 hr. with a solution of potassium hydroxide (1 g.) in water (2 ml.) and ethanol (8 ml.). After cooling, acidification caused liberation of hydrogen sulphide and precipitation of the acid, which was taken up in ether, extracted with sodium hydrogen carbonate solution, and reprecipitated with dilute hydrochloric acid. Yield: 55 mg. (74%) of ferrocenylacetic acid, identical with the above product in m. p. and infrared spectrum.

β-*Ferrocenylpropionic Acid.*—(a) *From ferrocenylacrylic acid.* A solution of β-ferrocenylacrylic acid [1] (0·1 g.) over 10% palladium on charcoal (0·03 g.) absorbed 9·5 ml. of hydrogen during 5 min. Evaporation of the filtered solution left β-ferrocenylpropionic acid (0·1 g.), m. p. 115—117·5°, raised by recrystallisation from *cyclo*hexane to 117—118° (lit.: [5, 6] 115—116°) (Found: C, 60·8; H, 5·6. Calc. for $C_{13}H_{14}O_2Fe$: C, 60·5; H, 5·5%).

(b) *From the quaternary salt* (IV). To a solution of sodium (0·3 g.; 0·013 mole) in absolute ethanol (50 ml.), diethyl malonate (5·5 g.; 0·035 mole) was added, followed by the quaternary salt (IV) (5 g.; 0·013 mole). The mixture was refluxed in a current of nitrogen for 5 hr. on a steam-bath. Most of the solvent was evaporated off under reduced pressure, water was then added, and the mixture extracted with ether. Evaporation of the dried ether solution left diethyl (ferrocenylmethyl)malonate as an oil which failed to crystallise and was therefore hydrolysed directly by heating on a steam-bath with 10N-sodium hydroxide. After all the ester had disappeared, the alkaline solution was cooled, neutralised, and extracted with ether. The ether solution was washed with water, dried, and evaporated, and the residue crystallised once from water. (Ferrocenylmethyl)malonic acid (0·7 g.; 18%) so obtained formed yellow leaflets, m. p. 144—145°, which decomposed on keeping and were not purified further. It was sublimed at 155°/0·3 mm. and then crystallised from ether at −78° to yield β-ferrocenylpropionic acid, m. p. 115°.

Similar results were obtained in another experiment when the reaction between diethyl sodiomalonate and the quaternary salt (IV) was carried out in *n*-butyl ether at 160° (8 hr.).[7] The m. p.s of both the above samples of ferrocenylpropionic acid were undepressed by admixture with an authentic specimen.[6]

*Diethyl (Ferrocenylmethyl)formamidomalonate* (VI).—The quaternary salt (IV) (5·01 g.; 0·013 mole) was added to a solution of diethyl sodioformamidomalonate, prepared by dissolving first sodium (0·6 g.; 0·026 mole) and then diethyl formamidomalonate (5·28 g.; 0·026 mole) in anhydrous ethanol (100 ml.). The mixture was refluxed and stirred for 19 hr. in a slow current of nitrogen. It was then filtered, and the solvent removed under reduced pressure. After addition of water to the residue, the mixture was extracted thrice with ether, and the ether solution dried and evaporated to leave an oil (5·17 g.) which solidified on cooling to −78°. Recrystallisation from aqueous ethanol gave yellow needles of *diethyl (ferrocenylmethyl)formamidomalonate* (3·81 g.; 73%), m. p. 90—91° (Found: C, 57·15; H, 6·2; N, 3·4, 3·65. $C_{19}H_{23}O_5NFe$ requires C, 56·9; H, 5·8; N, 3·5%).

*(Ferrocenylmethyl)formamidomalonic Acid* (VII).—The above ester (VI) (1 g.) was refluxed for 1·5 hr. with a solution of sodium hydroxide (1 g.) in water (7 ml.) and ethanol (9 ml.). The cooled reaction mixture was acidified with dilute hydrochloric acid and filtered, and the residue washed well with water. Recrystallisation from acetone–ligroin (b. p. 60—80°) afforded pale yellow crystals of *(ferrocenylmethyl)formamidomalonic acid* (0·43 g.; 50%), m. p. 160—161° (Found: C, 52·2; H, 4·7; N, 3·6. $C_{15}H_{15}O_5NFe$ requires C, 52·2; H, 4·4; N, 4·1%).

DL-*Ferrocenylalanine* (III).—(a) *From* (VI). The ester (VI) (0·44 g.) was refluxed with 6N-hydrochloric acid (12 ml.) under nitrogen for 45 min. (oil-bath temp. 125°). Evaporation of the cooled solution under reduced pressure yielded the crude hydrochloride (0·26 g.; 76%). This was dissolved in water and titrated to pH *ca.* 7 with 0·1N-sodium hydroxide. The precipitated DL-*ferrocenylalanine* (DL-α-amino-β-ferrocenylpropionic acid) (III) recrystallised from water as a yellow monohydrate, m. p. 290° (decomp.) (Found: C, 53·4; H, 5·9; N, 5·1. $C_{13}H_{15}O_2NFe,H_2O$ requires C, 53·6; H, 5·9; N, 4·8%). The same product was obtained in lower overall yield by the two-step hydrolysis of (VI) to (VII) as described above, followed by refluxing (VII) with 2N-hydrochloric acid (2 hr.).

(b) *From* (II). No hydrolysis took place when the *cyclo*hexylformamido-derivative (II) of

[6] Woodward and Csendes, personal communication; cf. refs. 4 and 5.
[7] Snyder, Smith, and Stewart, *J. Amer. Chem. Soc.*, 1944, **66**, 200.

XUM

the amino-acid was dissolved in 0·1N-lithium hydroxide, brought to pH 8·1 with 0·1N-phosphate buffer, and incubated with carboxypeptidase for up to 72 hr. When refluxed (8 hr.) with 50% sodium hydroxide, 60% of (II) was recovered unchanged and only a trace of unidentified ninhydrin-positive product formed. Complete destruction of all but 5% of (II) occurred on heating with water at 140—160° for 6 hr. Refluxing with 2N-hydrochloric acid appeared to have no effect on (II), but when this acid (0·3 g.) was heated (17 hr.) in a sealed tube with 6N-hydrochloric acid (10 ml.) and *n*-butanol (10 ml.) and the aqueous layer which separated on cooling was neutralised with ammonia, it yielded DL-ferrocenylalanine (4 mg.) after evaporation to dryness and extraction with *n*-butanol.

The authors thank Dr. K. Schlögl for keeping them informed of his parallel investigations.[2] They are indebted to the Minnesota Mining and Manufacturing Company for a grant, and to E.I. du Pont de Nemours & Co. for gifts of ferrocene.

THE UNIVERSITY, SHEFFIELD 10. [*Received, July 19th*, 1957.]

---

## 129. *The Kinetics of the Oxidation of Ethane by Nitrous Oxide.*

By R. KENWRIGHT, P. L. ROBINSON, and A. B. TRENWITH.

The oxidation of ethane by nitrous oxide has been investigated between 530° and 670° and at pressures of 25—250 mm. The rate is measurable above 530°, at which temperature ethane decomposes and nitrous oxide is stable. The principal products are hydrogen, nitrogen, methane, carbon monoxide, and ethylene; small amounts of carbon dioxide and formaldehyde appear, but water, ethanol, and acetaldehyde were not detected. Initial-rate measurements indicate an empirical rate equation which is consistent with a mechanism involving the reactions generally accepted as occurring in the decomposition of ethane, together with certain others.

Formaldehyde, acetaldehyde, propionaldehyde, dimethyl ether, and diethyl ether have been separately pyrolysed in the presence of nitrous oxide. The reaction products indicate that of all the radicals produced under our experimental conditions, only ethyl reacts with nitrous oxide, so this, leading to the ethoxy-radical and nitrogen, is concluded to be the primary oxidation step in the ethane–nitrous oxide system.

The results throw light on the mode of decomposition of diethyl ether as they indicate that ethyl radicals are produced in the initial stages of its decomposition.

HYDROGEN [1] and methane [2] are oxidised by nitrous oxide above 600° by chain processes. Each oxidation depends upon the thermal decomposition of nitrous oxide, the first step being the formation of atomic oxygen; this subsequently attacks the hydrogen or methane molecules. A qualitative examination showed that the normal paraffins from propane to nonane [3] reacted with nitrous oxide well below 600°, at which nitrous oxide is stable. It was suggested that all the reactions proceeded by chain processes resulting from a splitting of the hydrocarbon molecule into two alkyl radicals which then attack a nitrous oxide molecule: $R\cdot + N_2O \longrightarrow RO\cdot + N_2$. The alkoxy-radical subsequently breaks down into an aldehyde molecule and alkyl radical or hydrogen atom in the accepted manner.

There is thus a clear difference between the behaviour towards nitrous oxide of methane on the one hand, and of propane and higher hydrocarbons on the other. We now consider how ethane reacts with nitrous oxide, and show that its behaviour is similar to that of propane and higher hydrocarbons.

[1] Melville, *Proc. Roy. Soc.*, 1933, *A*, **142**, 524; 1934, *A*, **146**, 737.
[2] Robinson and Smith, *J.*, 1952, 3895.
[3] Smith, *J.*, 1953, 1271.

## Experimental

*Materials.*—Nitrous oxide (anæsthesia grade) was dried ($P_2O_5$) and collected in a trap cooled in liquid nitrogen. Non-condensable gases were pumped off and the residue was purified by fractionation between −130° and −196° (head and tail fractions being rejected) and stored. Ethane, from a cylinder (Petrochemicals Ltd.), was frozen in a trap cooled in liquid nitrogen; after non-condensable gases had been pumped off, it was distilled in a low-temperature Podbielniak-type column. A middle cut of the fraction, b. p. −88°, was collected. Formaldehyde, prepared by Spence and Wild's method,[4] was kept at −196° until required. Acetaldehyde of reagent quality was purified by distillation from anhydrous sodium sulphate. A middle cut of the fraction, b. p. 21°, was vacuum-distilled into the apparatus and stored at −85°. Propionaldehyde, after the addition of 1 drop of concentrated sulphuric acid to 20 ml. of the liquid, was distilled. A middle cut of the fraction, b. p. 49°, was vacuum-distilled to a trap on the apparatus and stored at −85°. Diethyl ether (B.P.C.) was distilled, a middle cut of the fraction, b. p. 34·5°, being vacuum-distilled into the apparatus and stored at −85°.

*Apparatus.*—Two cylindrical silica reaction vessels were used, one empty, 15 × 4·5 cm., with a 1 : 1 surface : volume ratio, and the other, 11 × 4 cm., packed with silica tubing, with a 9 : 1 surface : volume ratio. Each had a thermocouple well and a capillary inlet and was connected to the rest of the system, which was of Pyrex glass, by a B7 cone and socket sealed with Picein wax. Evacuation was by a mercury-vapour pump backed by a rotary oil pump. The reaction vessel was embedded in a tubular electric furnace kept to within ±0·2° of the required temperature by a Sunvic resistance thermometer controller, type R.T.2. The temperture was measured by means of a chromel–alumel thermocouple and Doran potentiometer.

A constant-volume mercury manometer [5] was used to measure pressures except when these changed rapidly, when a simple U-manometer was more convenient. A two-way tap enabled the reaction vessel to be connected in turn to two sampling bulbs.

The reaction vessel was also connected through a capillary tap to a series of five traps. The first four were empty and the last contained activated charcoal. They were connected separately to a form of gas burette which might be used either as a Töpler pump or a McLeod gauge, so that volumes of 0·01 to 30 ml. could be measured with an accuracy of ±0·1%. The gas burette was connected to a pipette containing mercuric sulphate in sulphuric acid (57 g. of $HgSO_4$ in 100 g. of 22% $H_2SO_4$) for the absorption of ethylene, a small bulb packed with Carbosorb for the removal of carbon dioxide, and a take-off point fitted with a B14 socket.

*Operation.*—The reaction between ethane and nitrous oxide was followed by both change of pressure with time and analysis of the products after various periods of heating. To observe the pressures, nitrous oxide followed immediately by ethane was admitted to the reaction vessel from the apportioning bulbs, and readings were taken at approximately half-minute intervals during the first 10 to 15 min. In an attempt to secure uniform surface conditions, the reaction vessel was first conditioned by doing a few runs and subsequently kept under a vacuum for 15 min. before individual experiments.

For analysis, the reaction vessel was connected to the collecting traps, cooled in liquid nitrogen, to which the contents were transferred in approximately 10—15 sec. Condensable materials were frozen out in the first four traps and non-condensable gases were adsorbed on activated charcoal in the last. This trap was later heated to 300°; the released gas was withdrawn into a sampling bulb fitted with a B14 cone and a tap, and analysed mass-spectrometrically.

The condensable products were transferred to the gas burette and measured. Carbon dioxide was removed by passage over the Carbosorb and ethylene by absorption in the mercuric sulphate–sulphuric acid solution. Because of the solubility of nitrous oxide in this reagent a small correction to the volume reading was necessary. This correction was ascertained by following the rate of absorption of the mixture by the reagent. A rapid initial take-up was observed followed by a slow but regular one, the latter due to absorption of nitrous oxide; by allowing for it, a reliable determination of ethylene could be made.

Water, ethanol, acetaldehyde, and formaldehyde were also sought among the products. To detect water, a U-tube containing phosphoric oxide was introduced between the furnace and the collecting traps. This was evacuated and weighed before and after the passage of the

[4] Spence and Wild, *J.*, 1935, 338.
[5] Dodd and Robinson, "Experimental Inorganic Chemistry," Elsevier, Amsterdam, 1954, p. 122.

XUM

products. To detect ethanol and acetaldehyde the condensable products were vacuum-fractionated between one trap at −135° and another at −196°. Ethanol and acetaldehyde, having negligible vapour pressures at −135°, tend to remain in the first trap.

To detect formaldehyde a separate apparatus was used in which a stream of purified ethane and nitrous oxide (approximately 1 : 1 at 1 atm.) was passed through a silica reaction vessel, heated to 580°, and fitted with a capillary inlet and outlet. The issuing gas was bubbled through a solution of chromotropic acid (50 mg. of sodium salt in 100 ml. of 75% $H_2SO_4$) at 60°.

Formaldehyde, acetaldehyde, propionaldehyde, and diethyl ether were separatedly pyrolysed both alone and in the presence of nitrous oxide. The initial rates of the reactions were measured and the products after various times of heating analysed.

## Results and Discussion

Ethane and nitrous oxide react measurably above 500°. A series of experiments, carried out between 530° and 670°, in which the pressure of either reactant was varied, gave pressure–time curves from which initial rates were derived. The effects on the rates of

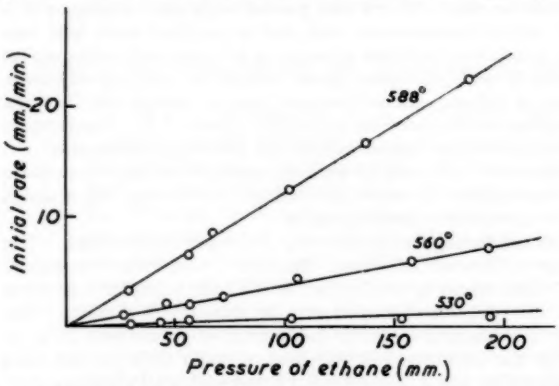



Fig. 1. *Variation of initial rate with pressure of ethane.* (*Pressure of* $N_2O$, 50 *mm.*)

variation of the pressure of each reactant are shown in Figs. 1 and 2. The results conform to the empirical rate equation:

$$\text{Rate} = k'[C_2H_6] + k''[C_2H_6][N_2O]$$

This relationship applied up to 670°, despite the appreciable rate of decomposition of nitrous oxide at this temperature—at 670° ethane decomposes so rapidly that any change in the rate of reaction caused by the decomposition of nitrous oxide is insignificant.

Fig. 3 shows the products from a mixture of ethane (100 mm.) and nitrous oxide (100 mm.) after various times of heating at 560°. In addition to the ethylene and hydrogen normally produced in the decomposition of ethane, appreciable quantities of nitrogen, carbon monoxide, methane, and carbon dioxide are present. The flow experiment indicated that formaldehyde is also formed, as a purple colour developed in the chromotropic acid solution after 2 min. which intensified with time. (Attempts to determine the formaldehyde were unsuccessful owing to its very small amount; ethane and nitrous oxide alone gave a blank.)

Repeated tests showed that water, ethanol, and acetaldehyde were always absent from the products.

These observations lead us to suggest the following mechanism for the reaction between ethane and nitrous oxide:

$$C_2H_6 \longrightarrow 2CH_3\cdot \quad . \quad . \quad . \quad (1)$$

$$CH_3\cdot + C_2H_6 \longrightarrow C_2H_5\cdot + CH_4 \quad . \quad (2)$$

$$C_2H_5\cdot \longrightarrow C_2H_4 + H\cdot \quad . \quad . \quad (3)$$

$$H\cdot + C_2H_6 \longrightarrow C_2H_5\cdot + H_2 \quad . \quad . \quad (4)$$

$$H\cdot + C_2H_5\cdot \longrightarrow C_2H_6 \text{ or } C_2H_4 + H_2 \quad (5)$$

$$C_2H_5\cdot + N_2O \longrightarrow C_2H_5O\cdot + N_2 \quad . \quad (6)$$

$$C_2H_5O\cdot \longrightarrow CH_3\cdot + CH_2O \quad . \quad (7)$$

It includes reactions (1)—(5) which are usually accepted as representing the decomposition of ethane, in addition to (6) and (7) which are discussed below. There is also the formation of carbon monoxide and hydrogen by the decomposition of the formaldehyde

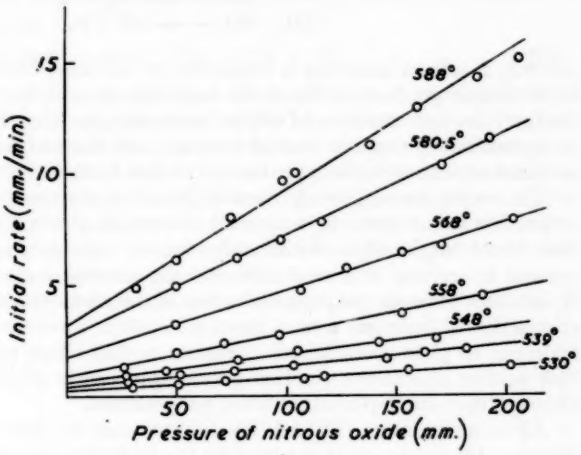



FIG. 2. *Variation of initial rate with pressure of nitrous oxide. (Pressure of* $C_2H_6 = 50$ *mm.)*

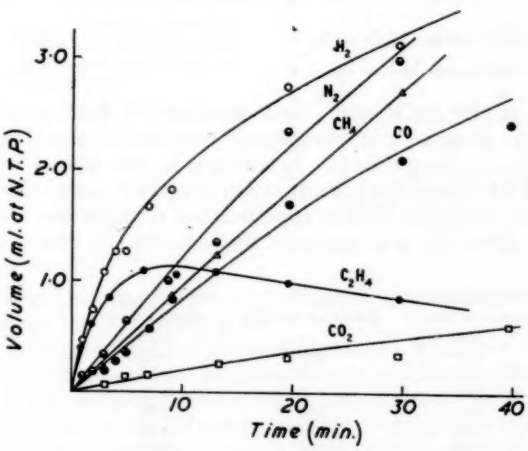



FIG. 3. *Products of pyrolysis of* 100 *mm. of ethane* +100 *mm. of* $N_2O$ *at* 560°.

produced in (7), a reaction catalysed by nitrous oxide (p. 666). Subsequently carbon dioxide results from reaction (8) which, as Bawn [6] has shown, takes place under our experimental conditions. The maximum in the ethylene–time curve is in accord with Steacie and McDonald's observations [7] that ethylene polymerised and decomposed when heated with nitrous oxide above 530°.

The mechanism suggested can be considered as including two simultaneous chain reactions. The chain-carrying steps of the first are (3) and (4) and lead to an equation (9) representing the decomposition of ethane. The chain-carrying steps of the second are

[6] Bawn, *Trans. Faraday Soc.*, 1935, **31**, 461.
[7] Steacie and McDonald, *Canad. J. Res.*, 1935, **12**, 711.

(6), (7), and (2) which, if the decomposition of the formaldehyde produced in (7) is rapid, yield eqn. (10). The inference that (8), (9), (10), and the polymerisation of ethylene are

$$CO + N_2O \longrightarrow CO_2 + N_2 \quad . . . . . (8)$$

$$C_2H_6 \longrightarrow C_2H_4 + H_2 \quad . . . . . (9)$$

$$C_2H_6 + N_2O \longrightarrow CO + H_2 + N_2 + CH_4 \quad . . . . . (10)$$

the only reactions occurring is supported by the analytical data. For instance, hydrogen is the major product as would be expected since it is produced in both (9) and (10). Further, the concentration of carbon monoxide plus that of carbon dioxide after any time is approximately equal to that of methane, and the carbon dioxide concentration plus the methane concentration is approximately equal to that of nitrogen.

The reason for suggesting reaction (5) as the chain-ending process is that, of a number of possible terminators, it is the only one which yields a theoretical equation resembling that found empirically. Incidentally, similar considerations have had to be taken into account in arriving at a mechanism for the thermal decomposition of ethane.[8] Reaction (7) has been given as the most likely fate of the ethoxy-radical; [9] other possibilities are the abstraction of hydrogen from a donor molecule to form ethanol, and the loss of an atom of hydrogen to yield acetaldehyde. Failure to find either ethanol or acetaldehyde suggests that neither alternative reaction occurs appreciably under our experimental conditions, although they are important at lower temperatures.[9]

Although reactions (11) and (12), said to occur in other systems,[1, 2] also appear feasible, reaction (12) can be ruled out because the hydroxyl radicals should form water, and none was found. To decide on the validity of (11) a mixture of acetaldehyde (100 mm.) and

$$CH_3\cdot + N_2O \longrightarrow CH_3O\cdot + N_2 \quad . . . . . (11)$$

$$H\cdot + N_2O \longrightarrow HO\cdot + N_2 \quad . . . . . (12)$$

nitrous oxide (100 mm.) was heated at 560° for 10 min. Since acetaldehyde decomposes in part, at least, by a chain mechanism involving methyl radicals,[10] reaction (11) would be indicated by the presence of nitrogen in the products. As nitrogen is also formed by oxidation of the carbon monoxide, if (11) occurs the amount of nitrogen must exceed that of the carbon dioxide found. A trace of carbon dioxide appeared, but nitrogen was not detected by the mass spectrometer. From this it is concluded that reaction (11) does not occur under these conditions.

| Temp. | Reactant | Reactant pressure (mm.) | $N_2O$ pressure (mm.) | $(dp/dt)_{init.}$ (mm./sec.) |
|---|---|---|---|---|
| 560° | $CH_3$·CHO | 100 | 0 | 0·32 |
| ,, | ,, | 100 | 100 | 0·85 |
| ,, | ,, | 190 | 0 | 0·86 |
| ,, | $C_2H_5$·CHO | 100 | 0 | 0·52 |
| ,, | ,, | 100 | 100 | 0·65 |
| ,, | $C_2H_5$·O·$C_2H_5$ | 95 | 0 | 0·42 |
| ,, | ,, | 95 | 100 | 0·94 |
| 587 * | $C_2H_6$ | 100 | 100 | 0·24 |
| 587 † | $C_2H_6$ | 100 | 100 | 0·21 |
| 531 | H·CHO | 50 | 0 | 0·03 [11] |
| ,, | H·CHO | 50 | 50 | 0·30 |

* Vessel not packed. † Vessel packed.

There is a marked increase in the rate of decomposition of acetaldehyde in the presence of nitrous oxide (see Table). This well-known accelerating effect is said [12] to be due to

[8] Trotman-Dickinson, " Gas Kinetics," Butterworths, 1955, p. 152.
[9] *Discuss. Faraday Soc.*, 1951, **10**, 242.
[10] Steacie, " Atomic and Free Radical Reactions," Reinhold, New York, 1956.
[11] Fletcher, *Proc. Roy. Soc.*, 1934, *A*, **146**, 357.
[12] Verhoek, *Trans. Faraday Soc.*, 1935, **31**, 1527.

reaction (13). That we were unable to detect nitrogen might be thought to preclude this mechanism, but under our experimental conditions the chain length of the aldehyde decomposition is very large (determinations of the hydrogen and methane produced by pyrolysis of acetaldehyde at 470° indicate a chain length [13] of approximately 1200), whence only a trace of nitrous oxide need react according to (13) markedly to increase the rate of acetaldehyde decomposition.

$$N_2O + CH_3{\cdot}CHO \longrightarrow N_2 + CH_3{\cdot} + OH{\cdot} + CO \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

In search of confirmatory evidence for reaction (6) a mixture of propionaldehyde (100 mm.) and nitrous oxide (100 mm.) was pyrolysed at 560° for various times. Propionaldehyde yields methyl and ethyl radicals and atomic hydrogen on pyrolysis,[10] but since we can rule out the possibility of a reaction between methyl or atomic hydrogen and nitrous oxide, any nitrogen produced must result from (6) and (8). The composition of the products, shown graphically in Fig. 4, indicates the formation of nitrogen at a rate which increases slightly with time and is greater than the rate of formation of carbon dioxide. This evidence strongly supports the validity of reaction (6).

The results of a similar series of experiments with diethyl ether are shown in Fig. 5.

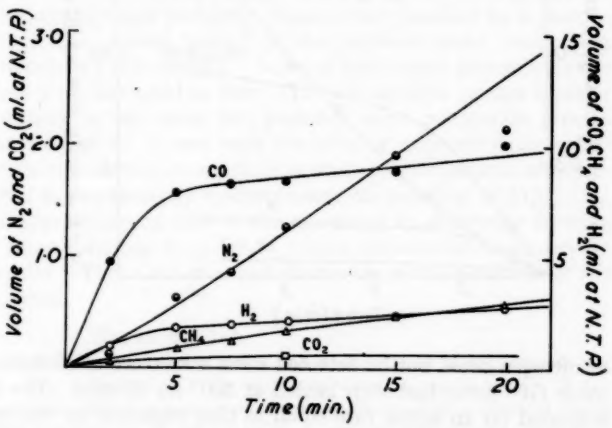



FIG. 4. *Products of pyrolysis of 100 mm. of propionaldehyde +100 mm. of nitrous oxide at 560°.*

Here also the nitrogen is produced in appreciable excess of the carbon dioxide, indicating again the probability of (6).

In connection with these observations, it has been borne in mind that ethane is produced by pyrolysis of both propionaldehyde and diethyl ether, so that nitrogen would be expected in the products. We consider, however, that the immediate appearance of nitrogen and the shape of the nitrogen–time curve suggest that the first-formed nitrogen is the result of a reaction between nitrous oxide and ethyl radicals from the parent organic molecule.

The theoretical rate equation derived from the mechanism given above is (14), which

$$\frac{-d[C_2H_6]}{dt} = \left(\frac{k_1k_3k_4}{k_5}\right)^{\frac{1}{2}}[C_2H_6] + \left\{k_6\left(\frac{k_1k_3k_4}{k_5}\right)^{\frac{1}{2}} \Big/ \left[k_3 - \left(\frac{k_1k_3k_5}{k_4}\right)^{\frac{1}{2}}\right]\right\}[C_2H_6][N_2O] \quad (14)$$

is identical in form with the empirical rate equation. The first term corresponds to the equation for the rate of decomposition of ethane alone so that $k'$, in the empirical rate equation, should correspond to the rate constant for the decomposition of ethane. The intercepts on the ordinate of the graphs in Fig. 2 are equal to $k'p_{\text{ethane}}$ and values for $k'$ can be derived from them. These yield the result $k' = 10^{13} \exp(-63{,}000/RT)$ sec.$^{-1}$, which is close to the accepted value for the ethane rate constant.[10]

[13] Trenwith, unpublished work.

It is concluded that in the main the reaction between nitrous oxide and ethane can be satisfactorily accounted for by assuming it to proceed by the chain decomposition of ethane together with a chain reaction resulting from the attack of ethyl radicals upon nitrous oxide. The actual mechanism is a little more complex than this since, as indicated in the Table, when carried out in a packed vessel the reaction is slower at first. (The present work was carried out in a conditioned vessel.)

The experiments with diethyl ether and nitrous oxide are of interest since two possible modes of decomposition of diethyl ether have been postulated,[10] one involving both methyl and ethyl radicals and the other only methyl radicals. Although our results do not entirely rule out the second mechanism, since they indicate the formation of ethyl radicals during the pyrolysis of diethyl ether, they support the first.

The rate of decomposition of diethyl ether is increased by the presence of nitrous oxide (Table). Experiments at a slightly lower temperature throw light on the reason for this

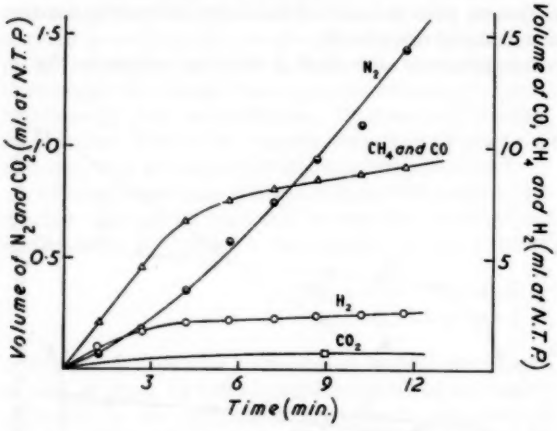



FIG. 5. *Products of pyrolysis of 100 mm. of diethyl ether +100 mm. of nitrous oxide at 560°.*

as nitrogen could not be detected when a mixture of diethyl ether (100 mm.) and nitrous oxide (100 mm.) had been heated at 500° for 15 min. The sigmoid pressure–time curve indicated (*a*) an initial rate equal to that expected for the decomposition of 100 mm. of diethyl ether alone, and (*b*) a subsequent increase in rate for about 10 min., followed by a steady decrease. This suggests that reaction (6) does not happen at this temperature, and that the action of nitrous oxide is restricted to catalysing the decomposition of acetaldehyde, the primary product.

In the reaction of nitrous oxide with formaldehyde, it is difficult to obtain accurate results because of the condensation of the formaldehyde. Nevertheless it is clear that nitrous oxide markedly increases the rate of decomposition of the formaldehyde (Table); however, the nitrous oxide is not altered as nitrogen is absent from the products which consist of hydrogen and carbon monoxide in equal amounts. The way in which formaldehyde decomposes is not yet known with certainty, but if it be by a free-radical chain mechanism then a reaction similar to (13) would account for the acceleration by nitrous oxide.

Nitrous oxide has less effect on the decomposition of these aldehydes on passing up the series. Thus with equimolar mixtures under similar conditions, the initial rate of decomposition is increased about ten times for formaldehyde, three times for acetaldehyde, and one and a quarter times for propionaldehyde.

The authors thank Mr. P. Kelly, M.Sc., for the mass-spectrometric determinations.

KING'S COLLEGE, NEWCASTLE UPON TYNE, 1. [*Received, July 29th,* 1957.]

## 130. *Solutions in Sulphuric Acid. Part XXIV.* Electrical Conductivity, Cryoscopic, and Density Measurements on Solutions in Dideuterosulphuric Acid.*

By R. H. Flowers, R. J. Gillespie, J. V. Oubridge, and C. Solomons.

Freezing points, and the densities and electrical conductivities at 25°, of the system $D_2O$–$SO_3$ have been measured in the region of the composition $D_2SO_4$ and of solutions of $KDSO_4$ and $NaDSO_4$ in 100% $D_2SO_4$. Some conductivities of the $D_2O$–$SO_3$ system and of solutions of $KDSO_4$ were also measured at 10° and 40°. The freezing point of $D_2SO_4$ is 14·35° ± 0·02°, its cryoscopic constant is 6·5, its specific conductance is $2{\cdot}568 \times 10^{-3}$ ohm$^{-1}$ cm.$^{-1}$, and its density ($d_4^{25}$) is 1·8573. From the results of the cryoscopic measurements the extent of self-dissociation of the solvent, and equilibrium constants for the reaction of $D_2O$ and $D_2S_2O_7$ with the solvent have been calculated. The degree of ionisation of *m*-nitrotoluene in $D_2SO_4$ was also investigated.

The ions $H_3SO_4^+$ and $HSO_4^-$ produced by the ionisation of acids and bases, respectively, in sulphuric acid have very abnormally high mobilities because they conduct by a proton-transfer mechanism. Although the general nature of the proton-transfer conduction process is clear, many of its details are still obscure. Some of the factors determining the rate of this conduction process were discussed in Part XII;[1] it involves proton transfer from an ion to a solvent molecule or *vice versa* and probably some orientation process involving ions and/or solvent molecules. It was with the hope of improving our knowledge of the mechanism of electrical conduction in sulphuric acid that the present measurement were made. In addition to conductivity measurements on solutions of $D_2O$, $SO_3$, $KDSO_4$, and $NaDSO_4$ in dideuterosulphuric acid it was necessary to determine freezing points and densities of the same solutions in order to obtain information necessary to interpret the conductivity results. The calculation and discussion of the mobilities of the ions $D_3SO_4^+$ and $DSO_4^-$ is deferred.

### Experimental

*Apparatus.*—The apparatus used for the freezing point and conductivity measurements has been described previously.[2,3a] The densities of a few solutions were measured with a 10 c.c. specific gravity bottle. Most of the density measurements were made by a float method in the apparatus shown in Fig. 1. It was permanently attached to a conductivity cell and filled from the cell by suction. Thus the density of every solution whose conductivity was measured could be found quickly and conveniently without exposing the solution to the atmosphere. This densitometer consisted of a vertical tube (*A*), 1·5 cm. in diameter, around whose upper part was wound a solenoid (*B*) consisting of 6000 turns of 36 s.w.g. enamelled copper wire. The float (*C*) was a thin-walled glass cylinder of length 10 cm. and diameter 0·5 cm. This was made to float upright by means of an iron pellet sealed into the lower end. A small piece of soft iron (*D*) was sealed into the upper end. The float had four sharp glass spikes (*E*) protruding from its lower end, in order to prevent the main body of the float from coming into contact with the walls of the float chamber; otherwise the effects of surface tension were serious. A small platinum point (*F*) was mounted in the lower part of the tube and when this was empty or when it contained a solution of sufficiently low density the flat bottom of the float rested on this point. The weight of the float could be adjusted by small rings of platinum wire (*G*) so that it sank in those solutions whose densities were to be measured. After the densitometer had been filled with such a solution, the current through the solenoid was adjusted until it was just sufficient to raise the float from the platinum point. This was repeated several times for each

* Part XXIII, Gillespie and Robinson, *J.*, 1957, 4233.

[1] Gillespie and Wasif, *J.*, 1953, 221.
[2] Gillespie, Hughes, and Ingold, *J.*, 1950, 2475.
[3] (*a*) Gillespie, Oubridge, and Solomons, *J.*, 1957, 1804; (*b*) Kunzler and Giauque, *J. Amer. Chem. Soc.*, 1952, **74**, 804.

XUM

solution, the float being observed by means of a telescope mounted outside a glass panel in the side of the water thermostat (at 25° ± 0·005°) in which the combined conductance cell-densitometer was suspended. The current through the solenoid was measured on a milliammeter reading up to 150 mA with an accuracy of 1 mA. The densitometer had a range of 0·02 g. cm.$^{-3}$ for any given weight on the float, and an accuracy of ±0·0002 g. cm.$^{-3}$. A calibration curve showing the relation between the current and the density was obtained (i) by using solutions of potassium sulphate in sulphuric acid whose densities had been accurately measured by using the 10 c.c. specific gravity bottle and (ii) by successively adding to the float small platinum rings weighing about 0·01 g. each and observing the current needed to raise the float after each addition. The agreement between the two methods was satisfactory. The instrument was re-calibrated periodically, but no significant changes were observed.

*Dideuterosulphuric Acid.*—Sulphur trioxide, prepared and purified as described previously,[3] was distilled slowly into deuterium oxide (Norske Hydro 99·97% $D_2O$), the reaction vessel being cooled in an ice–salt bath. The reaction is vigorous, but not violent, below 0°. The composition of the product was found approximately from the weight of deuterium oxide taken and the weight of acid formed.

FIG. 1. *Densitometer.*

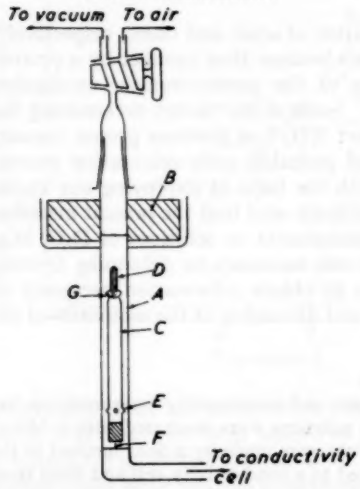
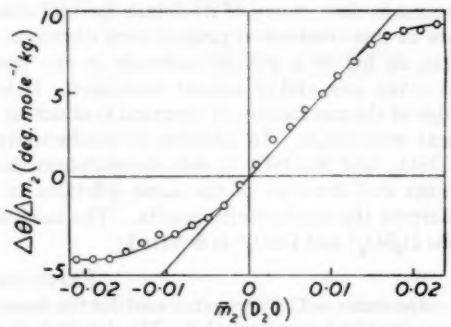



FIG. 2. *Plot for determining the degree of dissociation of $D_2SO_4$.*




*Potassium and Sodium Sulphates.*—" AnalaR " salts were dried at 150° for 2 hr. and stored in a desiccator over phosphoric oxide.

*Experimental Procedure.*—The combined conductivity–freezing-point measurements on the $D_2O$–$SO_3$ system were carried out as for the $H_2O$–$SO_3$ system.[3] For the conductivity measurements on solutions of $K_2SO_4$ and $Na_2SO_4$ the solvent was initially adjusted to the composition 100% $D_2SO_4$ by making small additions of a dilute solution of $D_2O$ in $D_2SO_4$ to a dilute oleum until it had the correct conductivity. Successive weighed portions of $K_2SO_4$ or $Na_2SO_4$ were then added to the solvent and the conductivity was measured. The freezing-point measurements on solutions of $K_2SO_4$ were made as previously described [4] after initially adjusting the solvent to maximum freezing point.

*Results.*—It is not possible to give all our many results in detail. The results of the measurements of the freezing point and of the conductivity at 25° in the immediate neighbourhood of the composition $D_2SO_4$ are shown graphically in Fig. 2. From a large-scale version of this plot and others covering larger concentration ranges, values of specific conductance and of freezing point were interpolated at round concentrations. These values are given in Tables 1 and 2, together with similar values for solutions of $KDSO_4$ and $NaDSO_4$.

The maximum freezing point, *i.e.*, the freezing point of $D_2SO_4$, is 14·35 ± 0·02°. The freezing point of $H_2SO_4$ is 10·37°. The error given is an estimate of the absolute error of the

[4] Gillespie and Oubridge, *J.*, 1956, 80.

measurements; the relative error was smaller and the maximum freezing point was generally found to be within a few thousandths of a degree of 14·347°; hence this is the value given in the Tables and used in the calculations. Fig. 2 shows that the minimum conductivity occurs on the oleum side of the composition $D_2SO_4$ and not on the aqueous side [3] as for $H_2SO_4$. The values of the composition of minimum conductivity at 25° and of the specific conductance at

TABLE 1. *Interpolated freezing points of solutions in dideuterosulphuric acid.*

| Concn. (m) | $D_2S_2O_7$ | $D_2O$ | $KDSO_4$ | Concn. (m) | $D_2S_2O_7$ | $D_2O$ | $KDSO_4$ | Concn. (m) | $D_2S_2O_7$ |
|---|---|---|---|---|---|---|---|---|---|
| 0·0000 | 14·347° | 14·347° | 14·347° | 0·0400 | 14·170° | 14·025° | 13·925° | 0·2000 | 13·100° |
| 0·0050 | 14·340 | 14·338 | — | 0·0600 | 14·044 | 13·803 | 13·681 | 0·2400 | 12·824 |
| 0·0100 | 14·325 | 14·317 | 14·263 | 0·0800 | 13·910 | 13·578 | 13·425 | 0·2800 | 12·550 |
| 0·0150 | 14·306 | 14·283 | — | 0·1000 | 13·777 | 13·352 | 13·173 | | |
| 0·0200 | 14·282 | 14·240 | 14·163 | 0·1200 | 13·645 | 13·135 | 12·916 | | |
| 0·0250 | 14·256 | 14·194 | — | 0·1450 | 13·508 | 12·920 | 12·660 | | |
| 0·0300 | 14·228 | 14·149 | 14·020 | 0·1600 | 13·370 | — | 12·401 | | |

TABLE 2. *Interpolated specific conductances of solutions in dideuterosulphuric acid at 25°.*

| Concn. | $\kappa$ ($10^{-2}$ ohm$^{-1}$ cm.$^{-1}$) | | | | Concn. | $\kappa$ ($10^{-2}$ ohm$^{-1}$ cm.$^{-1}$) | | | |
|---|---|---|---|---|---|---|---|---|---|
| (mole kg.$_{soln.}^{-1}$) | $D_2O$ | $D_2S_2O_7$ | $KDSO_4$ | $NaDSO_4$ | (mole kg.$_{soln.}^{-1}$) | $D_2O$ | $D_2S_2O_7$ | $KDSO_4$ | $NaDSO_4$ |
| 0·000 | 0·2568 | 0·2568 | 0·2568 | 0·2568 | 0·08 | 0·898 | 0·403 | 0·940 | 0·912 |
| 0·002 | 0·2596 | 0·2546 | — | — | 0·09 | 0·988 | 0·423 | 1·033 | 1·003 |
| 0·004 | 0·2645 | 0·2541 | — | — | 0·10 | 1·075 | 0·443 | 1·124 | 1·100 |
| 0·006 | 0·2700 | 0·2542 | — | — | 0·12 | 1·251 | 0·479 | 1·310 | 1·264 |
| 0·008 | 0·2775 | 0·2553 | — | — | 0·14 | 1·421 | 0·511 | 1·487 | 1·480 |
| 0·010 | 0·2862 | 0·2572 | 0·300 | 0·300 | 0·16 | 1·587 | 0·543 | 1·660 | 1·591 |
| 0·015 | 0·3130 | 0·2640 | 0·326 | 0·326 | 0·18 | 1·750 | 0·574 | 1·829 | 1·742 |
| 0·020 | 0·345 | 0·272 | 0·368 | 0·368 | 0·20 | 1·91 | 0·603 | 1·99 | 1·89 |
| 0·025 | 0·378 | 0·282 | 0·405 | 0·405 | 0·25 | 2·30 | 0·670 | 2·37 | 2·23 |
| 0·03 | 0·420 | 0·292 | 0·452 | 0·452 | 0·30 | 2·65 | 0·727 | 2·73 | 2·54 |
| 0·04 | 0·518 | 0·316 | 0·549 | 0·547 | 0·35 | 2·98 | 0·779 | 3·06 | 2·82 |
| 0·05 | 0·616 | 0·337 | 0·642 | 0·639 | 0·40 | 3·29 | 0·827 | 3·37 | 3·07 |
| 0·06 | 0·711 | 0·378 | 0·740 | 0·733 | 0·45 | 3·58 | 0·870 | 3·65 | 3·29 |
| 0·07 | 0·807 | 0·381 | 0·835 | 0·823 | 0·50 | 3·85 | 0·909 | 3·91 | 3·51 |

TABLE 3. *Specific conductances at the composition $D_2SO_4$ and at the composition of minimum conductance.*

| Temp. | $\kappa$ ($10^{-2}$ ohm$^{-1}$ cm.$^{-1}$) $D_2SO_4$ | $\kappa$ ($10^{-2}$ ohm$^{-1}$ cm.$^{-1}$) "Minimum" | Composition at minimum conductance (moles of $D_2S_2O_7$ kg.$_{soln.}^{-1}$) |
|---|---|---|---|
| 10·0° | 0·133 ± 0·001 | — | — |
| 25·0 | 0·2568 ± 0·0005 | 0·2540 ± 0·0005 | 0·0045 ± 0·001 |
| 40·0 | 0·446 ± 0·001 | — | — |

TABLE 4. *Interpolated specific conductances of solutions of potassium deuterium sulphate at 10° and 40°.*

| Concn. | $\kappa$ ($10^{-2}$ ohm$^{-1}$ cm.$^{-1}$) | | | Concn. | $\kappa$ ($10^{-2}$ ohm$^{-1}$ cm.$^{-1}$) | | |
|---|---|---|---|---|---|---|---|
| (mole kg.$_{soln.}^{-1}$) | 10° | 40° | $\kappa_{25°}/\kappa_{10°}$ | (mole kg.$_{soln.}^{-1}$) | 10° | 40° | $\kappa_{25°}/\kappa_{10°}$ |
| 0·00 | 0·133 | 0·448 | 1·93 | 0·12 | 0·854 | 1·91 | 1·53 |
| 0·02 | 0·220 | 0·600 | 1·67 | 0·14 | 0·977 | 2·18 | 1·53 |
| 0·04 | 0·346 | 0·847 | 1·58 | 0·16 | 1·08 | 2·43 | 1·54 |
| 0·06 | 0·474 | 1·11 | 1·56 | 0·18 | 1·19 | 2·67 | 1·54 |
| 0·08 | 0·601 | 1·37 | 1·56 | 0·20 | 1·30 | 2·89 | 1·53 |
| 0·10 | 0·727 | 1·64 | 1·54 | | | | |

this composition and at 100% $D_2SO_4$ are given in Table 3. A few rather less accurate observations were made at 10° and 40° in the immediate neighbourhood of the composition $D_2SO_4$. The values of the specific conductance at this composition at the temperatures 10° and 40° are also given in Table 3. The results of the measurements of the conductivities of solutions of $KDSO_4$ at 10° and 40° are given in Table 4 together with values of the ratio $\kappa_{25°}/\kappa_{10°}$ which are needed in a following paper.

XUM

Interpolated values of the densities of solutions of $D_2O$, $D_2S_2O_7$, $KDSO_4$, and $NaDSO_4$ at 25° are given in Table 5.

TABLE 5. *Interpolated densities of solutions in dideuterosulphuric acid at 25°.*

| Concn. | $d_4^{25}$ | | | | Concn. | $d_4^{25}$ | | |
|---|---|---|---|---|---|---|---|---|
| (mole kg.$_{soln.}^{-1}$) | $D_2O$ | $D_2S_2O_7$ | $KDSO_4$ | $NaDSO_4$ | (mole kg.$_{soln.}^{-1}$) | $D_2S_2O_7$ | $KDSO_4$ | $NaDSO_4$ |
| 0·00 | 1·8573 | 1·8573 | 1·8573 | 1·8573 | 0·25 | 1·8628 | 1·8742 | 1·8726 |
| 0·02 | 1·8574 | 1·8576 | 1·8583 | 1·8582 | 0·30 | 1·8642 | 1·8778 | 1·8757 |
| 0·04 | 1·8575 | 1·8580 | 1·8597 | 1·8595 | 0·35 | 1·8654 | 1·8813 | 1·8789 |
| 0·06 | 1·8576 | 1·8585 | 1·8610 | 1·8607 | 0·40 | 1·8668 | 1·8850 | 1·8821 |
| 0·08 | 1·8577 | 1·8588 | 1·8624 | 1·8620 | 0·45 | 1·8682 | 1·8886 | 1·8853 |
| 0·10 | 1·8578 | 1·8692 | 1·8637 | 1·8632 | 0·50 | 1·8695 | 1·8922 | 1·8888 |
| 0·15 | 1·8580 | 1·8604 | 1·8672 | 1·8663 | 0·60 | 1·8721 | 1·8993 | 1·8950 |
| 0·20 | 1·8582 | 1·8615 | 1·8707 | 1·8694 | | | | |

## DISCUSSION

*The Self-dissociation of Dideuterosulphuric Acid: Preliminary Estimate.*—Dideuterosulphuric acid self-dissociates in the same way as sulphuric acid [5] according to the equation

$$2D_2SO_4 = D_2O + D_2S_2O_7 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

As shown later, $D_2O$ is extensively ionised according to the equation

$$D_2O + D_2SO_4 = D_3O^+ + DSO_4^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

but $D_2S_2O_7$ is only slightly ionised. The overall dissociation reaction can therefore be written to a good approximation as

$$3D_2SO_4 = D_3O^+ + DSO_4^- + D_2S_2O_7 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

According to Wyatt [6] the extent of dissociation $\alpha$ of a solvent dissociating according to the equation

$$n\mathrm{C} = \mathrm{A}(\longrightarrow a \text{ particles}) + \mathrm{B}(\longrightarrow b \text{ particles})$$

is

$$\alpha = -k_f abn/(a + b)m_1 (\partial^2 T/\partial m_2^2)_{m_2=0} \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

For the dissociation given in eqn. (3), $a = 2$, $b = 1$, and $n = 3$, hence eqn. (4) becomes

$$a = -2\ k_f/m_1\ (\partial^2 T/\partial m_2^2)_{m_2=0} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where $k_f$ is the cryoscopic constant of the solvent, $m_1$ the molality of the solvent, $m_2$ the molality of the solute, and $T$ the freezing point. The value of $(\partial^2 T/\partial m_2^2)_{m_2=0}$ can be found by plotting $\Delta\theta/\Delta m_2 = -\Delta T/\Delta m_2$ against $\overline{m_2}$. This has been done with the freezing points given in Fig. 2, and the resulting plot is shown in Fig. 3. The slope at $m_2 = 0$, *i.e.*, $(\partial^2 T/\partial m_2^2)_{m_2=0}$ is $-5{\cdot}5 \times 10^2$ deg. kg.$^2$ mole$^{-2}$. Hence from eqn. (5), taking $k_f = 6{\cdot}5$ (p. 672), we find that $\alpha = 2{\cdot}4 \times 10^{-3}$. Hence the total concentration of dissociation products, $m_x$, is 0·024m, and therefore

$$[D_3O^+] = [D_2S_2O_7] = [DSO_4^-] = 8 \times 10^{-3}\mathrm{m}$$

Thus

$$K_d = [D_3O^+][DSO_4^-][D_2S_2O_7] = 5{\cdot}1 \times 10^{-7} \text{ mole}^3 \text{ kg.}^{-3}$$

The total depression of the freezing point produced by the products of the self-dissociation is given by $\delta = k_f m_d = 0{\cdot}155°$. Hence, if the self-dissociation can be represented by eqn. (3), the theoretical freezing point of the hypothetical undissociated acid is $T_0' = 14{\cdot}50_3°$.

[5] Gillespie, *J.*, 1950, 2516.
[6] Wyatt, *Trans. Faraday Soc.*, 1956, **52**, 806.

*The Cryoscopic Constant and the Heat of Fusion.*—A value for the cryoscopic constant of dideuterosulphuric acid can be obtained from the results of our measurements on the freezing points of solutions of potassium sulphate, which may be assumed to be fully ionised, by assuming that the deviations from ideal behaviour in solutions of $K_2SO_4$ in $D_2SO_4$ are the same as in solutions of $K_2SO_4$ in $H_2SO_4$ at the same ionic strength.

The general equation [4] relating the freezing-point depression $\theta$ to the molality $m_2$ of the solute is

$$\theta/m_2 = g\nu k_f\{1 - (1/T_0 - \Delta C_p/2\Delta H_0^f)\theta\}\{1 + (2s - \nu)m_2/2m_1\} \quad . \quad . \quad (6)$$

where $\nu$ is the number of moles of ions and molecules formed in solution by one mole of the solute, $k_f$ is the cryoscopic constant, $g$ is the osmotic coefficient, $T_0$ is the freezing point of the pure solvent, $\Delta C_p$ is the difference between the heat capacities of the solid and the liquid solvent, $\Delta H_0^f$ is the heat of fusion of the pure solvent, and $s$ is the number of moles of solvent required to react with one mole of the solute. If we assume that $\Delta C_p$ and $\Delta H_0^f$ have the same value as for $H_2SO_4$, which is very likely to be a reasonably good approximation and will not therefore cause any error because $(1/T_0 - \Delta C_p/2\Delta H_0^f)\theta \ll 1$, we obtain

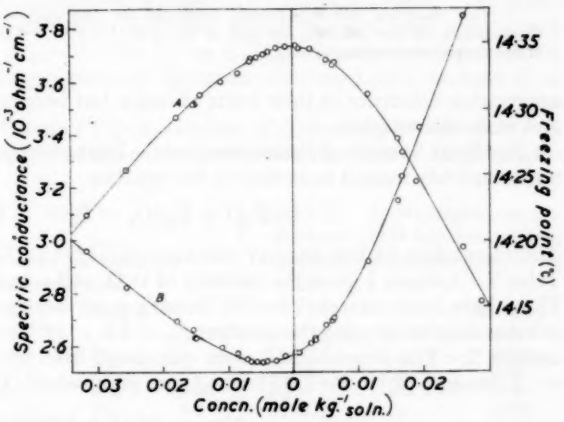



FIG. 3. *Freezing points and specific conductances in the region of the composition* $D_2SO_4$.
Curve *A*: Freezing-point depression.
Curve *B*: Specific conductance.

a value of 0·0018 for the term $(1/T_0 - \Delta C_p/2\Delta H_0^f)$. Since $K_2SO_4$ ionises according to the equation

$$K_2SO_4 + D_2SO_4 = 2K^+ + 2DSO_4^-$$

we have $s = 1$ and $\nu = 4$, and since also $m_1 = 9{\cdot}99$ we can write

$$\theta/m_2 = 4gk_f(1 - 0{\cdot}0018\theta)(1 - m_2/9{\cdot}99) \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Now if we substitute for $\theta$, $m_2$, and $g$, using values of $g$ for solutions of $K_2SO_4$ in $H_2SO_4$ at the same total ionic strength (allowing for the contribution of the self-dissociation products), we obtain the values of $k_f$ given in Table 6 and hence the mean value $k_f = 6{\cdot}47$ deg. mole$^{-1}$ kg. The accuracy of this value is difficult to assess because the reliability of the method by which it was obtained is uncertain. It seems probable, however, that $k_f = 6{\cdot}5 \pm 0{\cdot}1$ deg. mole$^{-1}$ kg. By substituting for $T_0$, $R$, and $m_1$ in the equation

$$k_f = RT_0^2/m_1\Delta H_0^f$$

we obtain the value of 2540 calories for the heat of fusion ($\Delta H_0^f$) of dideuterosulphuric acid. Within the rather uncertain accuracy of the above method of determining this quantity it cannot be said to differ significantly from the heat of fusion of $H_2SO_4$ ($\Delta H_0^f = 2560$ cal. mole$^{-1}$).

Some calorimetric measurements were also made which showed within a rather large

experimental error that the heats of fusion of $H_2SO_4$ and $D_2SO_4$ are approximately the same. The method used was to drop a sample of the acid ($H_2SO_4$ or $D_2SO_4$) in a sealed tube at 0° into a calorimeter consisting of a Dewar flask containing water, and to observe the decrease in temperature that this produced. Owing to relatively large errors in cooling corrections the results were not of sufficient accuracy to warrant their detailed presentation.

The cryoscopic constants of $H_2SO_4$ and $D_2SO_4$ thus appear to differ not because of any

TABLE 6. *Calculation of the cryoscopic constant.*

| Concn. (m) $KDSO_4$ | F. p. (obs.) | F. p.* (corr.) | $\theta$ | $gk_f$ | $\mu^{\frac{1}{2}}$ | $g$ | $k_f$ | |
|---|---|---|---|---|---|---|---|---|
| 0·00 | 14·347° | 14·502° | — | — | — | — | — | |
| 0·02 | 14·160 | 14·248 | 0·254° | 6·34 | 0·1549 | 0·982 | 6·47 | |
| 0·04 | 13·922 | 13·989 | 0·513 | 6·43 | 0·2073 | 0·985 | 6·53 | |
| 0·06 | 13·678 | 13·732 | 0·770 | 6·44 | 0·2510 | 0·991 | 6·50 | |
| 0·08 | 13·422 | 13·468 | 1·034 | 6·49 | 0·2863 | 0·997 | 6·51 | Mean, |
| 0·10 | 13·170 | 13·212 | 1·290 | 6·49 | 0·3193 | 1·002 | 6·48 | 6·47 |
| 0·12 | 12·913 | 12·951 | 1·551 | 6·51 | 0·3493 | 1·009 | 6·46 | |
| 0·14 | 12·657 | 12·691 | 1·811 | 6·53 | 0·3770 | 1·015 | 6·43 | |
| 0·16 | 12·398 | 12·430 | 2·072 | 6·55 | 0·4025 | 1·022 | 6·42 | |

* The observed freezing points corrected for the depression due to the products of the self-dissociation of the solvent, by use of $K_d = 5{\cdot}1 \times 10^{-7}$. The depressions $\theta$ were calculated from these corrected freezing points.

appreciable difference in their heats of fusion but because of their different freezing points and molecular weights.

*The Basic Strength of Deuterium Oxide.*—Deuterium oxide is extensively but apparently not completely ionised according to the equation

$$D_2O + D_2SO_4 = D_3O^+ + DSO_4^-$$

The calculation of the basicity constant $K_b(D_2O) = [D_3O^+][DSO_4^-]/[D_2O]$ is set out in Table 7. Column 1 gives the molality of $D_2O$, and column 2 the observed freezing points. These have been corrected for the freezing-point depression produced by the products of self-dissociation by using the constant $K_d = 5{\cdot}1 \times 10^{-7}$ and the corrected values are given in column 3. The depressions $\theta$ were calculated from these values. If we set $s = 1$ and $\nu \sim 2$ [see eqn. (2)] in the final term of eqn. (6) it reduces to

$$\theta/m_2 = g\nu k_f(1 - 0{\cdot}00018\theta) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

from which the values of $g\nu$ were calculated. The necessary estimates for $g$ were made by taking the values [4] for $K_2SO_4$ in $H_2SO_4$ at the same total ionic strength, $D_2O$ being assumed fully ionised. This assumption was made in order to make some allowance for the effect of the un-ionised part of the $D_2O$ on the osmotic coefficient $g$, which, because it is undoubtedly solvated by forming hydrogen bonds with solvent molecules, might be expected to be similar in its effect to $D_3O^+$ at the relatively high concentrations with which we are concerned. These values of $g$ are given in column 6. Hence the values of $\nu$ were obtained. Finally $K_b$ was calculated from the expression

$$K_b = (\nu - 1)[DSO_4^-]/(2 - \nu)$$

The mean value is $K_b = 0{\cdot}23$.

*The Acid Strength of Dideuterodisulphuric Acid.*—The calculation of the acid dissociation constant of dideuterodisulphuric acid is set out in Table 8. No adequate allowance can be made for non-ideality in this case so the osmotic coefficient $g$ was set equal to unity at all concentrations. The assumption made previously that the dideuterodisulphuric acid produced in 100% acid by the self-ionisation reaction is not ionised is not a sufficiently good approximation for solutions of dideuterodisulphuric acid, the self-dissociation being, in fact, repressed to a greater extent than this assumption would predict. Owing to the difficulty of allowing adequately for the repression of the self-dissociation, values of $\nu$, and

hence of $K_a$, have only been calculated for concentrations of 0·08m and greater, for which it is certain that the self-dissociation is more than 70% repressed, and they have been calculated by assuming that the self-dissociation is completely repressed. The acid dissociation constant $K_a$ was calculated from the expression $K_a = (\nu - 1)^2 m/(2 - \nu)$ and the approximate constancy of the value obtained suggests that the various assumptions

TABLE 7. *Calculation of the basic dissociation constant of deuterium oxide.*

| Concn. (m) | F. p. (obs.) | F. p. (corr.) | $\theta$ | $g\nu$ | $g$ | $\nu$ | $K_b$ | |
|---|---|---|---|---|---|---|---|---|
| 0·00 | 14·347° | 14·502° | — | — | — | — | — | |
| 0·02 | 14·237 | 14·260 | 0·242° | 1·87 | 0·981 | 1·91 | 0·20 | |
| 0·04 | 14·030 | 14·036 | 0·466 | 1·80 | 0·984 | 1·83 | 0·16 | |
| 0·06 | 13·803 | 13·806 | 0·696 | 1·79 | 0·980 | 1·81 | 0·21 | Mean |
| 0·08 | 13·578 | 13·580 | 0·922 | 1·78 | 0·996 | 1·79 | 0·24 | 0·23 |
| 0·10 | 13·353 | 13·354 | 1·148 | 1·77 | 1·002 | 1·76 | 0·24 | |
| 0·12 | 13·135 | 13·135 | 1·367 | 1·76 | 1·008 | 1·75 | 0·27 | |
| 0·14 | 12·920 | 12·920 | 1·582 | 1·75 | 1·014 | 1·72 | 0·26 | |

and approximations on which the calculation is based are reasonably valid. The mean value of $K_a = 2 \times 10^{-3}$ shows that dideuterodisulphuric acid is an appreciably weaker acid in $D_2SO_4$ than disulphuric acid ($K_a = 2 \times 10^{-2}$) [7] in $H_2SO_4$. In aqueous solution the substitution of deuterium for hydrogen generally decreases the dissociation constant of an acid by a factor of three to four.[8]

*An Improved Estimate of the Extent of Self-dissociation of Dideuterosulphuric Acid.*—It was assumed earlier in the calculation of the extent of the self-dissociation of dideutero-

TABLE 8. *Calculation of the acid dissociation constant of dideuterodisulphuric acid.*

| Concn. (m) | F. p. | $\theta$ | $\nu$ | $10^3 K_a$ | |
|---|---|---|---|---|---|
| 0·00 | (14·502°) | — | — | — | |
| 0·08 | 13·910 | 0·592° | 1·15 | 2·1 | |
| 0·12 | 13·645 | 0·857 | 1·12 | 1·9 | |
| 0·16 | 13·370 | 1·132 | 1·10 | 2·2 | Mean |
| 0·20 | 13·100 | 1·402 | 1·10 | 2·2 | 2·4 |
| 0·24 | 12·824 | 1·678 | 1·10 | 2·7 | |
| 0·28 | 12·550 | 1·952 | 1·10 | 3·1 | |

TABLE 9. *Approximate concentrations of the self-dissociation products of dideuterosulphuric acid.*

| | Molality |
|---|---|
| $DSO_4^-$ ..... | 0·010 |
| $D_2SO_4^+$ ..... | 0·004 |
| $DS_2O_7^-$ ..... | 0·004 |
| $D_3O^+$ ..... | 0·010 |
| $D_2S_2O_7$ ..... | 0·006 |
| Total ..... | 0·034 |

sulphuric acid that the dideuterodisulphuric acid ($D_2S_2O_7$) produced by the self-dissociation is not ionised. This is only a rough approximation and, by using the value of the dissociation constant of dideuterodisulphuric acid calculated above, the calculation of the concentrations of the self-dissociation products of dideuterosulphuric acid can be somewhat improved. The concentration of dideuterodisulphuric acid produced by the self-dissociation being 0·008m, from the acid dissociation of dideuterodisulphuric acid ($K_a = 2 \times 10^{-3}$) the degree of dissociation of a solution of dideuterodisulphuric acid having this stoicheiometric concentration is readily shown to be 40%. It is reasonable to assume that the dideuterodisulphuric acid produced in the self-dissociation reaction is ionised approximately to the same extent. If allowance is made in eqn. (4) for the ionisation of dideuterodisulphuric acid by putting $a = 1{\cdot}4$ and $n = 3{\cdot}4$ it is found that the total concentration of self-dissociation products is 0·033m and that the individual concentrations of self-dissociation products are as given in Table 9. From these concentrations values of the autodeuterolysis constant $K_{ad}$ and the ionic self-dehydration constant $K_{id}$ can be calculated; $K_{ad} = [D_3SO_4^+][DSO_4^-] = K_{id} = [D_3O^+][DS_2O_7^-] = 4 \times 10^{-5}$ mole$^2$ l.$^{-2}$.

[7] Gillespie, *J.*, 1950, 2493.
[8] See, for example, Gurney, "Ionic Processes in Solution," McGraw-Hill, London, 1953.

XUM

*The Ionisation of* m-*Nitrotoluene.*—The ionisation of weak bases in sulphuric acid has been studied previously [9,10,11,12] and it was therefore of interest to compare the extent of ionisation of a weak base in dideuterosulphuric acid with its degree of ionisation in sulphuric acid. *m*-Nitrotoluene was chosen, and the results of the measurements of the conductivity of its solutions in dideuterosulphuric acid are given in Table 10. The

TABLE 10. *Specific conductances of solutions of* m-*nitrotoluene at* 25°.

| Concn. (mole $kg._{soln.}^{-1}$) ..... | 0·0000 | 0·0109 | 0·1205 | 0·1952 | 0·2698 | 0·3690 |
|---|---|---|---|---|---|---|
| $\kappa$ ($10^{-3}$ $ohm^{-1}$ $cm.^{-1}$) ..... | 0·257 | 0·272 | 0·402 | 0·574 | 0·638 | 0·695 |

conductivity of its solutions changed very slowly with time although over the period of 2 hr. during which the measurements recorded in Table 10 were made this drift in the conductivity was quite negligible: it could be caused by the deuteration of the *m*-nitrotoluene which would be expected to be very slow under the experimental conditions. By comparing the conductivities with those of $KDSO_4$ solutions (Table 2) the degree of ionisation of *m*-nitrotoluene at various concentrations could be calculated by the method of Gillespie and Solomons [11] and hence values of $K_b = [R{\cdot}NO_2D^+][DSO_4^-]/[R{\cdot}NO_2]$ were obtained. The mean value was $K_b$ ($D_2SO_4$) = 0·012 mole $kg.^{-1}$ which can be compared with the value $K_b$ ($H_2SO_4$) = 0·023 mole $kg.^{-1}$ given by Gillespie and Solomons.[11] Thus *m*-nitroluene is less ionised in $D_2SO_4$ than in $H_2SO_4$ and this can probably be attributed to $H_2SO_4$ being a slightly stronger acid than $D_2SO_4$. The alternative explanation that $CH_3{\cdot}C_6H_4{\cdot}NO_2D^+$ is a stronger acid than $CH_3{\cdot}C_6H_4{\cdot}NO_2H^+$ seems less probable since it is generally found that substitution of hydrogen by deuterium reduces the strength of an acid.

We thank the London County Council for a major County Scholarship (to C. S.) and the Ministry of Education for a grant (to R. F.).

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER ST., LONDON, W.C.1. [*Received, September 9th,* 1957.]

[9] Gillespie, *J.*, 1950, 2542.
[10] Brand, Horning, and Thornley, *J.*, 1952, 1374.
[11] Gillespie and Solomons, *J.*, 1957, 1796.
[12] Gillespie and Robinson, *J.*, 1957, 4233.

---

## 131. *The Tautomerism of* N-*Heteroaromatic Hydroxy-compounds. Part III.*[1] *Ionisation Constants.*

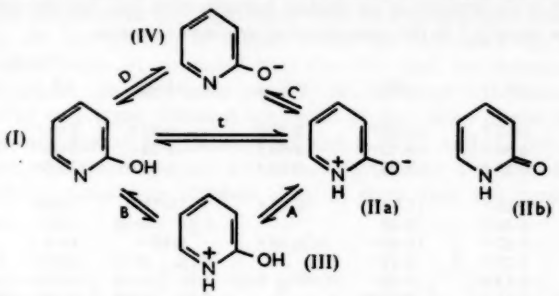
By S. F. MASON.

Acidic and basic ionisation constants are reported for a number of *N*-heteroaromatic hydroxy-compounds and their *O*- and *N*-methyl derivatives. From the measured and from published values, tautomeric equilibrium constants ($K_t$ = [NH form]/[OH form]) have been estimated for the mono-aza-compounds, and for the diaza-compounds with not more than one nitrogen atom conjugated with the hydroxyl group. For the diaza-compounds with a ring-nitrogen atom placed both *ortho* and *para* to the hydroxyl group, the equilibrium constant ($K_{op}$ = [*ortho*-quinonoid NH form]/[*para*-quinonoid NH form]) has been similarly estimated. Such constants have been found to agree, to within an order of magnitude, with those determined spectrophotometrically.[1] The ionisation and tautomeric constants are shown to vary with the π-electron energies of the species in equilibrium.

THE equilibrium constant ($K_t$) of the tautomerism of *N*-heteroaromatic hydroxy-compounds (*e.g.*, I ⇌ II) in aqueous solution to NH forms of a zwitterionic (*e.g.*, IIa) or an amide (*e.g.*, IIb) character may be measured spectrophotometrically [1] if the value of the constant lies in the range $10^2$—$10^{-2}$. For larger or smaller values, $K_t$ may be evaluated

[1] Part II, Mason, *J.*, 1957, 5010.

by a more general method from the ionisation constants of a given compound and those of its *O*- and *N*-methyl derivatives,[2,3] as for amino-acids.[4] The empirical ionisation constants ($K_1$ and $K_2$) of a *N*-heteroaromatic hydroxy-compound are composite, and they are related




to the true constants of the NH- ($K_A$ and $K_C$) and the OH-tautomer ($K_B$ and $K_D$) by the expressions:

$$K_1 = K_A + K_B \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$1/K_2 = 1/K_C + 1/K_D \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

since the tautomers of a given compound (*e.g.*, I and II) form a common cation (*e.g.*, III) by displacement of the equilibria (A) and (B), and a common anion (*e.g.*, IV) by displacement of the equilibria (C) and (D). The basic ionisation constants of the NH- and OH-tautomers ($K_A$ and $K_B$ respectively) may be assumed to equal approximately the constants of the *N*-methyl ($K_{NMe}$) and the *O*-methyl derivative ($K_{OMe}$) respectively, so that the tautomeric constant ($K_t$) and the acidic ionisation constants of the tautomers ($K_C$ and $K_D$ respectively) may be calculated by means of equations (2) and (3):

$$K_t = [\text{NH-form}]/[\text{OH-form}] = K_A/K_B = K_D/K_C = K_{NMe}/K_{OMe} \quad . \quad (3)$$

If the basic ionisation constant of a *N*-heteroaromatic hydroxy-compound ($K_1$) and that of only one of its *O*- or *N*-methyl derivatives is known, $K_t$ may be calculated by equations (4) or (5):

$$K_t = K_{OMe}/K_1 - 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$K_t = 1/(K_{NMe}/K_1 - 1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The ionisation constants of a number of *N*-heteroaromatic hydroxy-compounds and their *O*- and *N*-methyl derivatives have been measured in the present study, and the true ionisation constants of the tautomers ($K_A$, $K_B$, $K_C$, and $K_D$) and the tautomeric constant ($K_t$) have been calculated by means of the above equations, (3) being used wherever possible in calculating $K_t$ (Tables 1 and 2). Hitherto, equation (4) has been used to afford the $K_t$ values of *N*-heteroaromatic hydroxy-compounds from ionisation-constant data,[2,3] though equations (4) and (5) probably give less accurate values for $K_t$ than does (3). The inductive, steric, and hyperconjugation effects of the methyl group on the ionisation constants of the *O*- and *N*-methyl derivatives of a given compound are probably of the same order in each derivative, and these effects will largely cancel out in calculations of a value for $K_t$ according to equation (3), but not according to (4) and (5). The steric effect of the methyl group is important in the compounds with a hydroxyl group $\alpha$ to a ring nitrogen atom (Table 1, compounds 1, 4, and 11) for in these cases the parent substance, which is known spectroscopically to exist very largely in the NH-form,[1] is a stronger base

[2] Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923.
[3] Albert and Phillips, *J.*, 1956, 1294.
[4] Cohn and Edsall, "Proteins, Amino-acids, and Peptides as Ions and Dipolar Ions," Reinhold, New York, 1943.

XUM

TABLE 1. *The ionisation ($K_1$ and $K_2$) and the tautomeric ($K_t$ = [NH-form]/[OH-form]) constants of some monoaza-heteroaromatic hydroxy-compounds, and the ionisation constants of their* O- *and* N-*methyl derivatives ($K_{OMe}$ and $K_{NMe}$ respectively) in water at 20°, and the charge density at the position of the nuclear nitrogen atom ($q_n$), and the carbon atoms vicinal to the nitrogen atom ($q_c$) in the corresponding arylmethyl anion.*

| No. | Compound | p$K_1$ | p$K_2$ | p$K_{OMe}$ | p$K_{NMe}$ | log $K_t$ I [d] | log $K_t$ II [h] | $q_n$ [k] | $q_c$ |
|---|---|---|---|---|---|---|---|---|---|
| | *Pyridines* | | | | | | | | |
| 1 | 2-Hydroxy | 0·75 [a] | 11·62 [a] | 3·28 [a] | 0·32 [a] | 2·96 [e] | — | 1·143 | 1·0 |
| 2 | 3-Hydroxy | 4·86 [a] | 8·72 [a] | 4·88 [a] | −4·96 [a] | −0·08 [a] | 0·10 | 1·0 | 1·143 |
| 3 | 4-Hydroxy | 3·27 [a] | 11·09 [a] | 6·62 [a] | 3·33 [a] | 3·29 [e] | — | 1·143 | 1·0 |
| | *Quinolines* | | | | | | | | |
| 4 | 2-Hydroxy | −0·36 [a] | 11·74 [a] | 3·17 [a] | −0·71 [a] | 3·88 [e] | — | 1·235 | 1·0 |
| 5 | 3-Hydroxy | 4·30 [a] | 8·06 | — | 5·42 ± 0·02 | −1·08 [f] | −1·19 | 1·0 | 1·059 |
| 6 | 4-Hydroxy | 2·27 [a] | 11·25 [a] | 6·65 [a] | 2·46 [a] | 4·19 [e] | — | 1·200 | 1·0 |
| 7 | 5-Hydroxy | 5·20 [a] | 8·54 [a] | — | 6·12 ± 0·04 | −0·86 [f] | −1·27 | 1·050 | 1·0 |
| 8 | 6-Hydroxy | 5·17 [a] | 8·88 [a] | 5·06 ± 0·05 | 7·15 ± 0·03 | −2·09 [e] | −1·85 | 1·0 | 1·059 |
| 9 | 7-Hydroxy | 5·48 [a] | 8·85 [a] | — | 5·56 ± 0·02 | 0·69 [f] | −0·37 | 1·059 | 1·0 |
| 10 | 8-Hydroxy | 5·13 [a] | 9·89 [a] | — | 6·81 ± 0·02 | −1·67 [f] | −1·46 | 1·0 | 1·050 |
| | *isoQuinolines* | | | | | | | | |
| 11 | 1-Hydroxy | −1·2 [a] | — | 3·05 [a] | −1·8 [a] | 4·85 [e] | — | 1·200 | 1·0 |
| 12 | 4-Hydroxy | 4·80 ± 0·03 | 8·68 ± 0·04 | — | 4·93 ± 0·03 | 0·46 [f] | 0·58 | 1·0 | 1·200 |
| 13 | 5-Hydroxy | 5·40 ± 0·02 | 8·45 ± 0·03 | — | 6·90 ± 0·04 | −1·45 [f] | −1·42 | 1·0 | 1·050 |
| 14 | 6-Hydroxy | 5·85 ± 0·03 | 9·15 ± 0·03 | — | 6·02 ± 0·03 | 0·32 [f] | 0·28 | 1·059 | 1·0 |
| 15 | 7-Hydroxy | 5·70 ± 0·01 | 8·88 ± 0·02 | — | 7·09 ± 0·01 | −1·37 [f] | −1·42 | 1·0 | 1·059 |
| 16 | 8-Hydroxy | 5·66 ± 0·01 | 8·40 ± 0·02 | — | 5·81 ± 0·02 | 0·38 [f] | −0·06 | 1·050 | 1·0 |
| | *Acridines* | | | | | | | | |
| 17 | 1-Hydroxy | 4·18 [b] | — | 4·19 [b] | — | −1·6 [g] | −1·40 [i] | 1·0 | 1·024 |
| 18 | 2-Hydroxy | — | — | — | — | — | 0·40 [j] | 1·118 | 1·0 |
| 19 | 3-Hydroxy | 4·21, [b] 5·52 | 8·81 [a] | 4·27 [b] | — | −0·8 [g] | −1·82 [i] | 1·0 | 1·029 |
| 20 | 4-Hydroxy | — | — | — | — | — | −0·52 [j] | 1·095 | 1·0 |
| 21 | 5-Hydroxy | −0·32 [a] | — | 7 [a] | — | 7 [a] | — | 1·286 | 1·0 |
| | *Phenanthridine* | | | | | | | | |
| 22 | 7-Hydroxy | 4·39 ± 0·03 [c] | 8·68 ± 0·04 [c] | — | — | — | < −1 [i] | — | — |

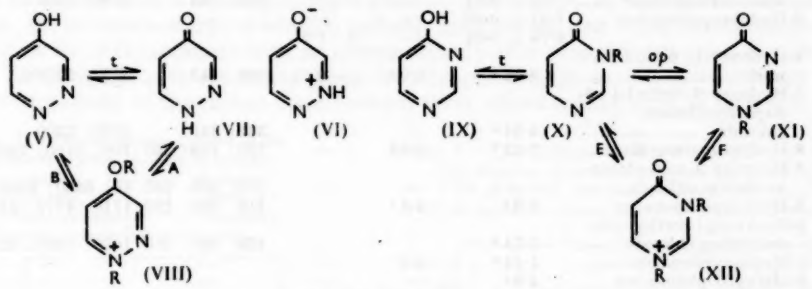
[a] Albert and Phillips, *J.*, 1956, 1294. [b] For 50% ethanol–water, from Albert, "The Acridines," Arnold, London, 1951, p. 114. [c] Determined spectroscopically at $5 \times 10^{-4}$M; analytical wavelengths 390 mμ and 385 mμ respectively. [d] Calc. from ionisation constants; present work. [e] Calc. by eqn. 3. [f] Calc. by eqn. 5. [g] For 50% ethanol–water, calc. by eqn. 4. [h] Determined spectroscopically; quoted from Part II. [i] For 1 : 9 ethanol–water. [j] For 1 : 4 ethanol–water. [k] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 275.

TABLE 2. *Ionisation constants of the* OH- *($K_B$ and $K_D$) and the* NH-*tautomers ($K_B$ and $K_C$) tautomers of the monoaza-heteroaromatic hydroxy-compounds in water at 20°, calculated from the results of Table* 1 *and equations* (1), (2), *and* (3).

| No. | Compound | p$K_A$ | p$K_B$ | p$K_C$ | p$K_D$ |
|---|---|---|---|---|---|
| 1 | 2-Hydroxypyridine | 0·75 | 3·71 | 11·62 | 8·66 |
| 2 | 3-Hydroxypyridine | 5·12 | 5·22 | 8·46 | 8·36 |
| 3 | 4-Hydroxypyridine | 3·27 | 6·56 | 11·09 | 7·80 |
| 4 | 2-Hydroxyquinoline | −0·31 | 3·57 | 11·74 | 7·86 |
| 5 | 3-Hydroxyquinoline | 5·52 | 4·33 | 6·84 | 8·03 |
| 6 | 4-Hydroxyquinoline | 2·27 | 6·46 | 11·25 | 7·06 |
| 7 | 5-Hydroxyquinoline | 6·49 | 5·22 | 7·25 | 8·52 |
| 8 | 6-Hydroxyquinoline | 7·03 | 5·18 | 7·02 | 8·87 |
| 9 | 7-Hydroxyquinoline | 6·01 | 5·64 | 8·32 | 8·69 |
| 10 | 8-Hydroxyquinoline | 6·60 | 5·14 | 8·42 | 9·88 |
| 11 | 1-Hydroxy*iso*quinoline | −1·2 | 3·6 | — | — |
| 12 | 4-Hydroxy*iso*quinoline | 4·90 | 5·48 | 8·58 | 8·00 |
| 13 | 5-Hydroxy*iso*quinoline | 6·84 | 5·42 | 7·01 | 8·43 |
| 14 | 6-Hydroxy*iso*quinoline | 6·04 | 6·32 | 8·95 | 8·67 |
| 15 | 7-Hydroxy*iso*quinoline | 7·14 | 5·72 | 7·44 | 8·86 |
| 16 | 8-Hydroxy*iso*quinoline | 5·99 | 5·93 | 8·07 | 8·13 |
| 17 | 3-Hydroxyacridine | 7·35 | 5·53 | 6·98 | 8·80 |
| 18 | 5-Hydroxyacridine | −0·32 | 7 | — | — |

than its *N*-methyl derivative, and the use of equation (5) gives a negative value for $K_t$. The superiority of equation (3) in general is illustrated by the cases in which $K_t$ may be calculated by all three equations and evaluated spectroscopically (Table 1, compounds 2 and 8), as equation (3) gives the best agreement with the spectroscopic value.

Equations (3), (4), and (5) may be used to afford the tautomeric equilibrium constants of diaza-compounds (Table 3), provided that the OH- and the dominant NH-tautomer form a common cation. In such cases (*e.g.*, V) two different NH-tautomers are possible (*e.g.*, VI and VII) and three different cations. It has been demonstrated [1] that the predominant NH-tautomer of 4-hydroxypyridazine is (VII), and the ultraviolet spectra of the cationic forms of 4-hydroxy- and 4-methoxy-pyridazine, 1-methyl-4-pyridazone, and 4-hydroxy-2-methylpyridazinium chloride (Fig. 1) show that the predominant cationic




structure is (VIII; R = H), as the first three compounds give almost identical absorption curves whilst the fourth has a quite different spectrum. Structure (VIII; R = H or Me) is the only one of the three possible cations which is common to 4-methoxypyridazine and 1-methyl-4-pyridazone, and exclusive of 4-hydroxy-2-methylpyridazinium chloride, so that the ratio of the ionisation constants of the first two compounds affords a measure of $K_t$ by equation (3). The diaza-compounds listed in Table 3 with not more than one nitrogen atom in the ring carrying the hydroxyl group are known to exist largely in the OH-form,[1,5] and since they are protonated and methylated on the same nitrogen atom, as the ultraviolet spectra of the cationic forms show (Table 3), a value for $K_t$ may be calculated by equation (5) in these cases. The measured ionisation constants of the diaza-compounds and the calculated tautomeric constants are listed in Table 3.

In the diaza-compounds with nitrogen atoms placed both $\alpha$ and $\gamma$ to the hydroxyl group (*e.g.*, IX) it has been shown spectroscopically that tautomerism occurs to two different NH-forms (*e.g.*, X and XI; R = H) with comparable stabilities.[6,7,8] In such cases $K_t$ cannot be calculated from the ionisation constants of the *O*- and the *N*-methyl derivative by equation (3), as these derivatives do not possess a common cation.[7,8] However, the parent substance (*e.g.*, IX) and its two *N*-methyl derivatives (*e.g.*, X and XI; R = Me) form cations with similar structures [7,8] (*e.g.*, XII; R = H or Me), so that the constant of the equilibrium between the two NH-tautomers ($K_{op}$) may be calculated from the ionisation constants of the two *N*-methyl derivatives by equation (6):

$$K_{op} = [\textit{ortho}\text{-quinonoid NH-form}]/[\textit{para}\text{-quinonoid NH-form}]$$
$$= K_E/K_F = K_{o\text{-NMe}}/K_{p\text{-NMe}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where $K_{o\text{-NMe}}$ and $K_{p\text{-NMe}}$ are the ionisation constants of the *ortho*- and the *para*-quinonoid *N*-methyl derivative respectively (*e.g.*, X and XI; R = Me).

[5] Part I, Mason, *J.*, 1957, 4874.
[6] Hearn, Morton, and Simpson, *J.*, 1951, 3318.
[7] Brown, Hoerger, and Mason, *J.*, 1955, 211.
[8] Brown and Mason, *J.*, 1956, 3443.

XUM

TABLE 3. *Ionisation* ($K_a$) *and tautomeric* ($K_t$ = [NH-]/[OH-*form*], *or* $K_{op}$ = [*ortho-quinonoid* NH-*form*]/[*para-quinonoid* NH-*form*]) *constants of some di- and poly-aza-heteroaromatic compounds in water at* 20°; *the ultraviolet absorption spectra of their cationic forms and of those of their* O- *and* N-*methyl derivatives.* (*Values in italics refer to shoulders.*)

| No. | Compound | p$K_a$ | log $K_t$ I | log $K_t$ II | $\lambda_{max.}$ (mμ) | $\varepsilon$ |
|---|---|---|---|---|---|---|
| 1 | 3-Hydroxypyridazine ... | −1·8 [a] | 4·3 [b] | — | 265 | 2560 |
| 2 | 3-Methoxypyridazine ..... | 2·52 [a] | — | — | 269 | 2010 |
| 3 | 4-Hydroxypyridazine ... | 1·07 [a] | 2·63 [b] | — | 245 | 8400 |
| 4 | 4-Methoxypyridazine ..... | 3·70 [a] | — | — | 247 | 10,320 |
| 5 | 1-Methyl-4-pyridazone ... | — | — | — | 252 [a] | 10,650 [a] |
| 6 | 4-Hydroxy-2-methylpyridazinium chloride ..... | 1·74 ± 0·04 | — | — | 271; 233 | 4290; 3850 |
| 7 | 5-Hydroxypyrimidine..... | 1·87 ± 0·03 | — | — | — | — |
| | | 6·78 ± 0·04 | — | ⩾−1·7 | | |
| 8 | 8-Hydroxy-1 : 6-naphthyridine ..... | 4·08 [b] | 0·09 | −0·05 | 328; 243 | 5660; 22,200 |
| 9 | 8-Hydroxy-6-methyl-1 : 6-naphthyridinium chloride ..... | 4·34 [b] | — | — | 332; 246 | 5750; 2300 |
| 10 | 8-Hydroxyquinazoline ... | 3·41 [b] | −3·85 | — | *370*; 298; 257 | *100*; 5480; 7000 |
| 11 | 8-Hydroxy-3-methylquinazolinium chloride ..... | — | — | — | *370*; 300; 261 | *86*; 6660; 6680 |
| 12 | 5-Hydroxyquinoxaline ... | 0·9 [b] | −4·8 [c] | — | 416; 338; 263 | 1110; 4770; 34,000 |
| 13 | 5-Hydroxy-1-methylquinoxalinium chloride ..... | 5·74 [b] | — | — | 426; 340; 264 | 1630; 5200; 32,000 |
| 14 | 1-Hydroxyphenazine ..... | 1·44 [c] | −3·5 [c] | — | — | — |
| 15 | 5-Methyl-1-phenazone ... | 4·9 [c] | — | — | — | — |
| 16 | 2-Hydroxyphenazine ..... | 2·6 [d] | −0·2 [c] | ⩾−0·6 | — | — |
| 17 | 10-Methyl-2-phenazone ... | 3·0 [d] | — | — | — | — |

| No. | Compound | p$K_a$ | log $K_{op}$ I | log $K_{op}$ II | $\lambda_{max.}$ (mμ) | $\varepsilon$ |
|---|---|---|---|---|---|---|
| 18 | 4-Hydroxypyrimidine..... | 1·85 [a] | 0·18 [j] | 0·40 [l] | 251; 224 [p] | 2970; 9840 [p] |
| 19 | 1-Methyl-4-pyrimidone ... | 2·02 ± 0·04 [e] | — | — | 252; 229 [p] | 2640; 10,200 [p] |
| 20 | 3-Methyl-4-pyrimidone ... | 1·84 [a] | — | — | 258; 226 [p] | 2940; 9080 [p] |
| 21 | 4-Hydroxyquinazoline ... | — | — | 0·85 [m] | — | — |
| 22 | 4-Hydroxypteridine ..... | −0·17 [f] | 1·72 [j] | >1 [n] | 303; 257 [q] | 9120; 2690 [q] |
| 23 | 1-Methyl-4-pteridone ..... | 1·25 [f] | — | — | 305; 263 [q] | 10,720; 3090 [q] |
| 24 | 3-Methyl-4-pteridone ..... | −0·47 [f] | — | — | 304; 265 [q] | 10,000; 2880 [q] |

[a] Albert and Phillips, *J.*, 1956, 1294. [b] Albert and Hampton, *J.*, 1954, 505. [c] Michaelis, Hill, and Schubert, *Biochem. Z.*, 1932, **255**, 70. [d] Preisler and Hempelmann, *J. Amer. Chem. Soc.*, 1937, **59**, 141. [e] Measured spectroscopically at 5 × $10^{-5}$M; analytical wavelengths, 240, 245, and 250 mμ. Brown and Mason, *J.*, 1956, 3443. [f] Calc. from ionisation constants; present work. [g] Calc. by eqn. 4. [h] Calc. by eqn. 5. [j] Calc. by eqn. 6. [k] Determined spectroscopically; from Part II. [l] Calc. from Fig. 2 of Brown, Hoerger, and Mason, *J.*, 1955, 211; analytical wavelength 240 mμ. [m] Calc. from the data of Hearn, Morton, and Simpson, *J.*, 1951, 3318. [n] Estimated from Fig. 2 of Brown and Mason, *J.*, 1956, 3443. [o] Staehelin, Eichenberger, and Druey, *Helv. Chim. Acta*, 1956, **39**, 1741. [p] Ref. 1. [q] Ref. *n*.

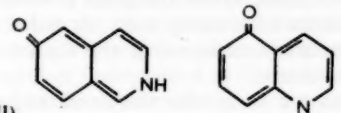
TABLE 4. *Charge density on the exocyclic atom* ($q_x$) *and the mobile bond order between the exocyclic atom and the nucleus* ($p_{xy}$) *of some arylmethyl anions.*

| Aryl | $q_x$ [a] | $p_{xy}$ [b] | Aryl | $q_x$ [a] | $p_{xy}$ [b] |
|---|---|---|---|---|---|
| Phenyl ..... | 1·572 | 0·635 | 1-Naphthyl ..... | 1·450 | 0·688 [c] |
| 2-Naphthyl ..... | 1·529 | 0·649 [c] | 9-Anthryl ..... | 1·286 | 0·747 |
| 4-Diphenylyl ..... | 1·516 | 0·66 [d] | *cyclo*Butadienyl ..... | 1·000 | 0·862 |

[a] Calc. by Longuet-Higgins's method (*J. Chem. Phys.*, 1950, **18**, 265). [b] Calc. by the Hückel method. [c] Wheland, *J. Amer. Chem. Soc.*, 1941, **63**, 2025. [d] Jacobs, *J.*, 1952, 292.

Values of $K_{op}$ for three compounds have been calculated from equation (6) or from the spectra of the compounds, the values obtained by the two methods agreeing satisfactorily for 4-hydroxypyrimidine (Table 3). All the $K_{op}$ values recorded are greater than unity, indicating that the *ortho*-quinonoid NH-forms (*e.g.*, X; R = H) are more stable than their *para*-quinonoid isomers (*e.g.*, XI; R = H) in aqueous solution. In non-polar solvents the *ortho*-quinonoid tautomer is similarly the more stable of the two forms.[5] The greater

stability is not due to *ortho*-quinonoid resonance, for in the series of *N*-heteroaromatic hydroxy-compounds generally, the NH-tautomers with *para*-quinonoid resonance structures (*e.g.*, XIII) are more stable [1] relatively to the corresponding enol tautomer, than their isomers with *ortho*-quinonoid resonance structures (*e.g.*, XIV), provided that the



(XIII) (XIV)

oxygen and nitrogen atoms are not linked to the same carbon atom. The NH-tautomers with an oxygen atom α to a ring-nitrogen atom (*e.g.*, II; and X, R = H) contain an amide group, the resonance energy of which is probably greater than that of the vinylogous amide group of the NH-tautomers with an oxygen atom γ to a ring-nitrogen atom (*e.g.*, VII; and XI, R = H), as in the amide group the nitrogen and the oxygen atom enhance the electronegativity of the carbon atom between them, allowing that atom to form π-bonds

FIG. 1. *The ultraviolet spectra of the cationic forms,* (——) *4-hydroxypyridazine,* (– – – –) *4-methoxypyridazine,* (. . . .) *1-methyl-4-pyridazone, and* (— · —) *4-hydroxy-2-methylpyridazinium chloride.*

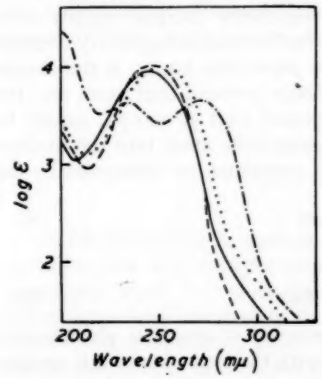
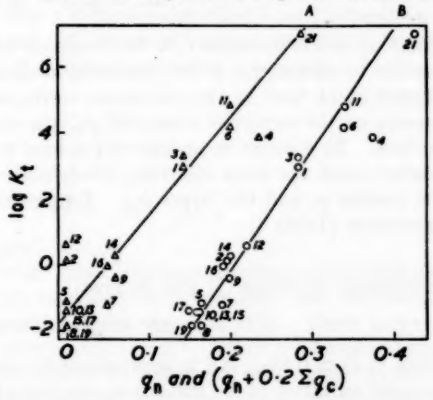



FIG. 2. (*A*) *Relation between* log $K_t$ *and* $q_n$. (*B*) *Relation between* log $K_t$ *and* $(q_n + 0{\cdot}2\Sigma q_c)$: 0·12 *of a unit has been added to the abscissa The numbers refer to the compounds in Table* 1.




more effectively with them. The greater energy of *para*-quinonoid resonance on the one hand and of amide resonance on the other nearly balance in determining the relative stabilities of compounds (X; R = H) and (XI; R = H), but on annelation and aza-substitution the aromatic π-electrons become progressively localised, so that the intrinsic amide group resonance becomes the more important factor. Thus in the series 4-hydroxypyrimidine, -quinazoline, and -pteridine the *ortho*-quinonoid form becomes increasingly the more stable of the two NH-tautomers (compounds 18, 21, 22, Table 3).

In the monoaza-series of *N*-heteroaromatic hydroxy-compounds the tautomeric equilibrium constants vary widely, covering a range of $10^9$ (Table 3). The ionisation constants of the NH-tautomers ($K_A$ and $K_C$) also cover a wide range, whilst those of the OH-tautomers ($K_B$ and $K_D$) show less variation (Table 2). The ionisation process governed by the constant, $K_D$ (*e.g.*, I ⇌ IV), is analogous to that of the aromatic phenols which show little variation of p$K_a$ with the nature of the aromatic nucleus and the position at which the hydroxyl group is attached. Thus phenol, 1- and 2-naphthol, and 1- and 2-anthranol have the p$K_a$ 9·96, 9·85, 9·93, 9·82, and 9·92 respectively.[9] A similar contrast

[9] Lauer, *Ber.*, 1937, **70**, *B*, 1288; Schenkel, *Experientia*, 1948, **4**, 383.

has been noted[10] between the two series of ionisation constants of the aromatic and the *N*-heteroaromatic amines respectively. The large differences between the ionisation constants of the *N*-heteroaromatic amines, covering a range[11] of $10^6$, have been ascribed[12] to the considerable variations in Coulombic energy, from one nuclear position to another, after protonation of a ring-nitrogen atom, whilst the small differences between the ionisation constants of the aromatic amines, covering only an order of magnitude, have been attributed[10] to the complementary variation of the Coulombic and the delocalisation energy in a series of such compounds.

Similar factors may be shown to govern the ionisation constants of aromatic and *N*-heteroaromatic hydroxy-compounds, and the tautomeric constants of the latter. In the aromatic phenols it is probable that the lone-pair electrons of the hydroxyl group are not extensively delocalised over the aromatic nucleus, owing to the large electronegativity difference between oxygen and carbon,[3] so that the Coulombic and the delocalisation energy do not vary greatly in the series. The $\pi$-electron energy of a phenol may be taken, approximately, to be that of the aromatic nucleus, whilst for the corresponding phenoxide ion there are two main additional $\pi$-energy terms, one due to the delocalisation of $\pi$-electrons into the Coulombic field of the oxygen atom and the other to the formation of the exocyclic $\pi$-bond. These terms vary in a series of phenoxide ions, the energy difference between a phenol and its anion, $\Delta E$, being given by the relation:

$$\Delta E = q_x\alpha_O + 2p_{xy}\beta_{OO} + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where $\alpha_O$ is the increment in the Coulomb integral of a negatively charged oxygen atom relative to carbon, $\beta_{OO}$ is the resonance integral between a carbon and a negatively charged oxygen atom, and, in the carbanion corresponding to the phenoxide ion, $q_x$ is the charge density on the exocyclic atom and $p_{xy}$ the mobile bond order between that atom and the nucleus. In a series of arylmethyl anions it may be expected that $q_x$ and $p_{xy}$ should be related, since the more electrons are delocalised from the exocyclic atom into the nucleus the smaller $q_x$ and the larger $p_{xy}$. Empirically these two quantities are connected by the expression (Table 4)

$$p_{xy} = -0{\cdot}4q_x + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Combining equations (7) and (8) gives:

$$\Delta E = q_x(\alpha_O - 0{\cdot}8\beta_{OO}) + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Thus, if $\alpha_O \simeq 0{\cdot}8\beta_{OO}$, $\Delta E$ is approximately constant in the series of aromatic phenols, and no great variation of the ionisation constant of the phenol with the type of aromatic nucleus or with the position of substitution of the hydroxyl group is to be expected, as variations in the delocalisation energy of the anion are compensated by converse variations in the Coulombic energy.

In the *N*-heteroaromatic hydroxy-compounds there should be a similar complementary variation of the Coulombic and the delocalisation energy accompanying the transfer of a proton from the exocyclic oxygen atom, so that the Coulombic energy change after protonation of the ring-nitrogen atom remains the major variable $\pi$-energy term governing the relative values of the tautomeric constants in this series. If it is assumed that the lone-pair electrons of the oxygen atom are extensively delocalised over the nucleus in the NH-tautomer (*e.g.*, II) as in the phenoxide ion, but not in the OH-tautomer (*e.g.*, I) as in a phenol, the difference in $\pi$-electron energy between the tautomers is given by the term, $q_n\alpha_{NH}$, where $\alpha_{NH}$ is the difference between the Coulomb integrals of the carbon atom and the protonated nuclear nitrogen atom, and $q_n$ is the charge density at the position of the latter atom in the corresponding arylmethyl anion. The relative tautomeric equilibrium

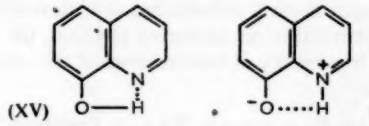
[10] Hush, *J.*, 1953, 684.
[11] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[12] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 275.

constants ($K_t$) in the series of *N*-heteroaromatic hydroxy-compounds should be governed, to a first approximation, by the variable π-energy term, $q_n\alpha_{NH}$, if the entropy change of the tautomerism is constant in the series.

It has been shown [1] that the entropy change of the tautomerism at a given temperature is reasonably constant in three of the four cases studied, and as the major contribution to the entropy change is probably the increase in order resulting from the solvation of the zwitterionic NH-tautomer (*e.g.*, IIa) no great variation of that change in the series is likely. Thus the relative free energies of tautomerism in the series and the π-energies of the NH-tautomers should be related by the expression:

$$RT \log K_t = q_n\alpha_{NH} + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

A plot of log $K_t$ against $q_n$ gives a fair straight line (Table 1, Fig. 2*A*) as equation (10) requires. The *ortho*- and *peri*-exceptions to the similar relation between $q_n$ and the p$K_a$ values of the *N*-heteroaromatic amines [12] have no analogues in the present series, owing to the self-cancellation of the inductive effect and hydrogen-bonding in the tautomerism of *N*-heteroaromatic hydroxy-compounds. In the case of 2-hydroxypyridine (I and II) the inductive effect of the nitrogen atom on the proton-releasing and -acepting properties of the oxygen atom should be of the same order as the reciprocal effect of the oxygen atom on the proton-donor and -acceptor properties of the nitrogen atom. Similarly, for 8-hydroxyquinoline both the OH-tautomer (XV) and the NH-tautomer (XVI) are intramolecularly hydrogen-bonded, so that the bonding has only a second-order effect [1] on the position of the tautomeric equilibrium (Table 1), whilst the p$K_a$ value of 8-aminoquinoline is lowered considerably by hydrogen-bonding,[11] as only the uncharged species is bonded.



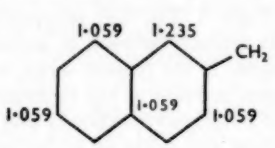

(XV) (XVI)

In the plot of log $K_t$ against $q_n$ (Fig. 2*A*) the "*meta*"-hydroxy-compounds, 3-hydroxypyridine and 4-hydroxy*iso*quinoline, though not 3-hydroxyquinoline, are anomalous, possessing larger $K_t$ values than expected according to equation (10). These large $K_t$ values have been ascribed to the inductive-electromeric effect.[1] When a nitrogen atom is substituted at an unconjugated (unstarred) position in the nucleus of an aromatic hydroxy-compound, both of the vicinal carbon atoms are in starred positions, bearing charge densities of greater than unity in the carbanion corresponding to the NH-tautomer. The electronegativity of such carbon atoms is increased inductively by the neutral nitrogen atom of the OH-tautomer and, more particularly, by the positively charged nitrogen atom of the NH-tautomer. Thus the carbon atoms vicinal to the nitrogen atom lower the energy of the NH-tautomer by a Coulombic contribution which varies with the position and the nucleus in which the nitrogen atom is substituted. The free energy of tautomerism may be related to this variable Coulombic energy term for the compounds in which the nitrogen atom is substituted in an unstarred position of the nucleus by the expression:

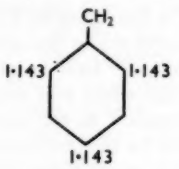
$$RT \log K_t = \sum q_c\alpha_O + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where $q_c$ is the charge on the vicinal carbon atoms in the corresponding carbanion, and $\alpha_O$ the increment in the Coulomb integral of the carbon atom when it is placed adjacent to a positively charged nitrogen atom, the sum being taken over vicinal carbon atoms. The values of $q_c$ for the arylmethyl anions corresponding to the three *meta*-hydroxy-*N*-heteroaromatic compounds considered are given in (XVII), (XVIII), and (XIX). The $q_c$ values of the carbon atoms adjacent to a nitrogen atom substituted *meta* to the exocyclic group in

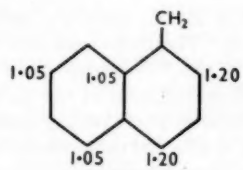
(XVIII) and (XIX) are large, so that, by equation (11), the Coulombic contributions to the stability of the corresponding NH-tautomers, those of 3-hydroxypyridine and 4-hydroxy-*iso*quinoline respectively, should be considerable. However, the charge densities on the carbon atoms vicinal to a nitrogen atom substituted at any unstarred secondary carbon atom position in (XVII) have the same small value, and the corresponding heteroanalogues, 3- and 6-hydroxyquinoline and 7-hydroxy*iso*quinoline, have tautomeric equilibrium constants of the same magnitude and smaller than those of 3-hydroxypyridine and 4-hydroxy*iso*quinoline (Table 1). The *N*-heteroaromatic hydroxy-compounds with the nitrogen atom substituted at an unstarred position in the nucleus are found to follow equation (11), log $K_t$ correlating linearly with $\sum q_c$ in these cases, and giving from the gradient of the relation a value of about 10 kcal./mole for $\alpha_C$ (Table 1).



(XVII)



(XVIII)



(XIX)

When a nitrogen atom is substituted in a starred position of the nucleus of an aromatic hydroxy-compound the vicinal carbon atoms are unstarred, carrying in all cases charge densities of unity in the corresponding arylmethyl anion. Thus the lowering of the Coulombic $\pi$-energy of the tautomers, due to the enhanced electronegativity of the vicinal carbon atoms, is a constant in these cases. The main variable $\pi$-energy term is given by equation (10) when the nitrogen atom is substituted in a starred nuclear position, and by equation (11) when it is substituted in an unstarred position, the combination of the two, equation (12), governing the free energy of tautomerism of the complete series of *N*-hetero-aromatic hydroxy-compounds:

$$\boldsymbol{RT} \log K_t = q_n\alpha_{NH} + \sum q_c\alpha_C + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad (12)$$

The Coulomb integral increment of a carbon atom adjacent to a positively charged nitrogen atom, $\alpha_C$, should be proportional to the increment of the latter atom, $\alpha_{NH}$, and empirically the experimental data may be best accommodated by the assumption that

$$\alpha_C = 0{\cdot}2\alpha_{NH} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

Combining equations (12) and (13) gives:

$$\boldsymbol{RT} \log K_t = \alpha_{NH}(q_n + 0{\cdot}2\sum q_c) + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad (14)$$

The plot of log $K_t$ against $(q_n + 0{\cdot}2\sum q_c)$ gives a satisfactory straight line (Fig. 2*B*) over the range of $K_t$ values from $10^{-2}$ to $10^3$, covering the compounds with a nitrogen atom substituted both at a starred and an unstarred position. The compounds with $K_t$ values $>10^3$ give points falling below the straight line (Fig. 2*B*), the NH-tautomers being less stable than expected according to equations (10) or (14). In these compounds the $\pi$-electron charge density on the nuclear nitrogen atom of the NH-tautomer, $q_n$, is large, so that this atom does not carry, even approximately, a net unit positive charge. Consequently the Coulomb integral increment, $\alpha_{NH}$, in such cases is smaller than that of a nitrogen atom bearing a unit positive charge, thus accounting by equations (10) and (14) for the observed trend in $K_t$ values when these are large. The slope of the line in Fig. 2*B* gives $\alpha_{NH}$ the value of about 50 kcal./mole and, by equation (13), $\alpha_C$ is equal to 10 kcal./mole, the latter agreeing with the value derived for $\alpha_C$ derived by equation (11).

The variation of the ionisation constants of the OH- and the NH-tautomer with the $\pi$-electron charge densities on the nuclear nitrogen atom, $q_n$, and the vicinal carbon atoms,

$q_c$ (Table 2, Figs. 3 and 4) in the series of monoaza-heteroaromatic hydroxy-compounds supports further the assumption that lone-pair electrons are extensively delocalised over the nucleus from a negatively charged, but not from a neutral, exocyclic oxygen atom. The free energy of the ionisation process governed by the constant, $K_A$ (*e.g.*, II $\rightleftharpoons$ III), may be equated to the right-hand side of equation (14), and a plot of log $K_A$ against $(q_n + 0{\cdot}2\sum q_c)$ should give a straight line of slope $\alpha_{HN}/RT$. A fair straight line is obtained (Fig. 3*A*) with a gradient giving $\alpha_{NH}$ the value of about 40 kcal./mole. The ionisation of the "*ortho*"-*N*-heteroaromatic hydroxy-compounds, unlike the tautomerism, is greatly influenced by the inductive effect and, for clarity, these compounds have been omitted from the plots of Figs. 3 and 4.

FIG. 3. (*A*) *Relation between* p$K_A$ *and* $(q_n + 0{\cdot}2\Sigma q_c)$. (*B*) *Relation between* p$K_B$ *and* $(q_n + 0{\cdot}2\Sigma q_c)$: 4 p$K$ *units have been added to the ordinate. The numbers refer to the compounds in Table* 2.

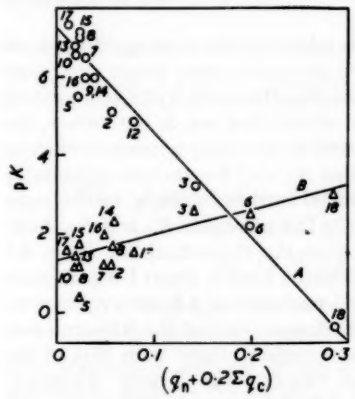
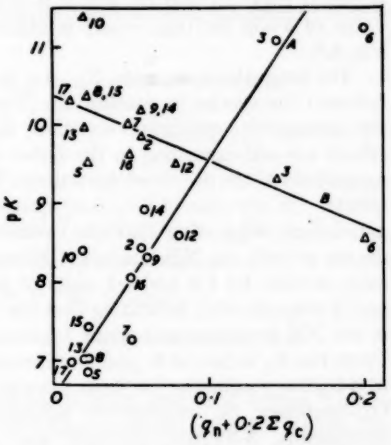



FIG. 4. (*A*) *Relation between* p$K_C$ *and* $(q_n + 0{\cdot}2\Sigma q_c)$. (*B*) *Relation between* p$K_D$ *and* $(q_n + 0{\cdot}2\Sigma q_c)$: 1·5 p$K$ *units have been substracted from the ordinate. The numbers refer to the compounds in Table* 2.




The free energy of the ionisation process governed by the constant, $K_C$ (*e.g.*, II $\rightleftharpoons$ IV), should vary in the series according to equation (15):

$$RT \log K_C = (\alpha_{NH} - \alpha_N)(q_n - 0{\cdot}2\sum q_c) + \text{Constant} \quad . \quad . \quad . \quad . \quad (15)$$

where $\alpha_N$ is the Coulomb integral increment of the neutral nitrogen atom. The relation between log $K_C$ and $(q_n + 0{\cdot}2\sum q_c)$ is reasonably linear (Fig. 4*A*), the slope giving $(\alpha_{NH} - \alpha_N)$ a value of about 37 kcal./mole. The $\pi$-energy change in the ionisation process governed by the constant, $K_B$ (*e.g.*, I $\rightleftharpoons$ III), should not vary in the series if the lone-pair electrons of the OH group are not delocalised at all, but the change may be equated to the right-hand side of equation (15) if these electrons are fully delocalised. The plot of log $K_B$ against $(q_n + 0{\cdot}2\sum q_c)$ gives a line (Fig. 3*B*) with a slight slope, from which an apparent value of 8 kcal./mole may be obtained for the quantity $(\alpha_{NH} - \alpha_N)$. This value is too small, but the fact that it is non-zero indicates that the lone-pair electrons of the OH group are delocalised to a small degree. The constant, $K_D$, of the remaining ionisation process (*e.g.*, I $\rightleftharpoons$ IV) should be governed by equation (16):

$$RT \log K_D = \alpha_N(q_n + 0{\cdot}2\sum q_c) + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad (16)$$

The plot of log $K_D$ against $(q_n + 0{\cdot}2\sum q_c)$ gives a fair straight line (Fig. 4*B*), from the slope of which a value of 12 kcal./mole for $\alpha_N$ may be obtained.

Expressed in terms of the Hückel carbon–carbon resonance integral, $\beta$, which has the

thermochemical value [14] of about 20 kcal./mole, the Coulomb integral increments obtained in the present work are $\alpha_{NH} = 2{\cdot}5\beta$ (from Fig. 2*B*, and from Figs. 4*A* and 4*B*), $\alpha_N = 0{\cdot}6\beta$ (from Fig. 4*B*), and $\alpha_O = 0{\cdot}5\beta$ [from equation (11) and from (13) and (14)]. The value of $0{\cdot}6\beta$ for $\alpha_N$ has been shown to give approximately the correct dipole moment of pyridine,[15] and it is now widely used in molecular-orbital treatments of *N*-heterocyclic molecules.[16] Values of $0{\cdot}64\beta$ for $\alpha_N$ and $0{\cdot}58\beta$ for $\alpha_O$ have been derived from the variation of the ionisation constants of the aromatic amines and diamines with the delocalisation energy and charge density on the exocyclic atom of the corresponding arylmethyl anions,[10] both values agreeing with those obtained in the present work. A value of $1{\cdot}2\beta$ for $(\alpha_{NH} - \alpha_N)$ has been obtained from the relation between the ionisation constants of the *N*-heteroaromatic amines and the charge density at the position of the nuclear nitrogen atom in the corrresponding arylmethyl anion,[12] though no allowance was made for the effect of the enhanced electronegativity of the carbon atoms adjacent to a ring-nitrogen atom on the $\pi$-energy of the species in equilibrium. The effect is relatively important (compare the slopes of Figs. 2*A* and *B*), and if it is allowed for in the *N*-heteroaromatic amine series a value of $1{\cdot}85\beta$ for $(\alpha_{NH} - \alpha_N)$ is obtained,[17] in agreement with the value derived from Fig. 4*A*.

The ionisation constants, $K_A$, $K_B$, $K_C$, and $K_D$, when related to the $\pi$-energy differences between the species in equilibrium (Figs. 3 and 4), give less satisfactory linear plots than the tautomeric equilibrium constant, $K_t$ (Fig. 2*B*). The inductive and hydrogen-bonding effects are self-cancelling in the latter equilibrium (see above), but not in the former, the magnitude of the observed deviations (Table 2, Figs. 3 and 4) providing a measure of these effects. In the case of 8-hydroxyquinoline, the constants $K_A$ and $K_B$ are not appreciably anomalous, suggesting that the cation is hydrogen-bonded intramolecularly to the same degree as both the NH- and the OH-tautomers (Fig. 3). The constants $K_C$ and $K_D$, however, deviate by 1·4 and 1·1 units of p$K$ respectively from the theoretical line (Figs. 4*A* and *B* respectively), indicating that the energy of the hydrogen bond is about 1·9 kcal./mole in the NH-tautomer and about 1·5 kcal./mole in the OH-tautomer of 8-hydroxyquinoline. From the $K_t$ values of 6- and 8-hydroxyquinoline, the hydrogen bond of the NH-tautomer of 8-hydroxyquinoline has been calculated [1] to be 0·5 kcal./mole stronger than that of the OH-tautomer, in satisfactory agreement with these values. The "*meta*"-hydroxy-compounds, 3-hydroxy-pyridine and -quinoline and 4-hydroxy*iso*quinoline, are more acidic in the ionisation processes (A), (B), and (D), though not (C), than expected from the $\pi$-energy differences between the species in equilibrium (Figs. 3 and 4). An inductive effect between the oxygen and the nitrogen atom through two carbon atoms is probable in these compounds, distinct from the inductive-electromeric effect of the carbon atoms adjacent to the ring-nitrogen atom. The relative magnitudes of the deviations from one ionisation process to another of the "*meta*"-hydroxy-compounds suggest that the inductive effect of the heteroatoms depends upon their charge in the order, $^+NH > OH > N > O^-$, and the absence of marked deviations in the ionisation process (C) indicate that the negatively charged oxygen atom has an electronegativity not greatly different from that of an $sp^2$ hybridised carbon atom (Table 2, Figs. 3 and 4). The deviations of the "*ortho*"-hydroxy-compounds (Table 2) suggest an alternative order for the inductive effect of the heteroatoms, $OH > {}^+NH > O^- > N$, the last pair having apparent electronegativities less than that of an $sp^2$ hybridised carbon atom. In the "*meta*"-hydroxy-compounds the nitrogen atom is substituted at an unstarred position in the nucleus, and so it is formally neutral in the anion and carries a formal unit positive charge in the NH-tautomer, according to first order perturbation theory. However, in the "*ortho*"-hydroxy-compounds the nitrogen atom is substituted at a starred position, so that it is

[13] Coulson and de Heer, *Trans. Faraday Soc.*, 1951, **47**, 681; *J.*, 1952, 483.
[14] Coulson, "Valence," Oxford Univ. Press, 1952.
[15] Chalvet and Sandorfy, *Compt. rend.*, 1949, **228**, 566; Lowdin, *J. Chem. Phys.*, 1951, **19**, 1323.
[16] Davies, *Trans. Faraday Soc.*, 1955, **51**, 449; Brown and Heffernan, *J.*, 1956, 4288.
[17] Unpublished result.

negatively charged in the anion (*e.g.*, IV) and carries less than a unit positive charge in the NH-tautomer (*e.g.*, II), according to the same approximation. The change in the order of the inductive effect of the heteroatoms on passing from the "*meta*"- to the "*ortho*"-hydroxy-compounds may be ascribed, therefore, to the reduced electronegativities of the nitrogen atoms in the anions and NH-tautomers of the "*ortho*"-compounds, owing to π-electron charge densities of greater than unity on those atoms.

### Experimental

Materials were as in Part I.[5]

Absorption spectra were measured with a Hilger Uvispek H700/305 Quartz Spectrophotometer, and aqueous solutions with pH values two units less than the p$K_1$ value of the compound examined.

Ionisation constants were determined by potentiometric titration at 20° under nitrogen, a Cambridge pH meter being used with glass and calomel electrodes. The ionisation constants of the *N*-heteroaromatic hydroxy-compounds were measured at M/250 and those of the *O*- and *N*-methyl derivatives at M/100, each value recorded (Tables 1 and 2) being the average of nine determinations.

The author thanks the Australian National University for a Research Fellowship.

Australian National University.
Chemistry Department, The University, Exeter. [*Received, July 18th*, 1957.]

---

## 132. *Fungicidal Activity and Chemical Constitution. Part V.*[1] *Synthesis of Some Substituted Quinolines.*

By D. Woodcock and (Miss) V. W. Rogers.

The preparation of 6-hydroxy-5-*n*-pentyl- and 7-chloro-8-hydroxy-5-*n*-pentyl-quinoline is described.

The fungistatic activity of the 5-*n*-alkyl-8-hydroxyquinolines, prepared earlier[1] in an attempt to improve the activity of 8-hydroxyquinoline against the mycelium of *Aspergillus niger* van Tiegh.,[2] followed the pattern normally encountered in such an homologous series.[3] It rose to a maximum at a chain length of 5 or 6 carbon atoms, though the addition of $Cu^{2+}$ markedly reduced the activity.[4] In order to confirm the rôle played by chelation in the fungicidal activity of 8-hydroxy-5-*n*-pentylquinoline, it was decided to prepare and test the isomeric 6-hydroxy-5-*n*-pentylquinoline, which should possess comparable lipoid solubility whilst being incapable of chelation with heavy metals.

Fries migration of *m*-chlorophenyl valerate at 165° gave butyl 4-chloro-2-hydroxyphenyl ketone as the main product, the orientation being established by oxidation with potassium permanganate to 4-chloro-2-hydroxybenzoic acid. The isomeric butyl 2-chloro-4-hydroxyphenyl ketone, oxidisable to 2-chloro-4-hydroxybenzoic acid, is also formed, in greater amount at lower temperature as in the case of the Fries reaction of *m*-tolyl valerate.[5] There was no formation of butyl 2-chloro-6-hydroxyphenyl ketone, which would involve preferential substitution of a sterically hindered *ortho*-position.

Clemmensen reduction of butyl 4-chloro-2-hydroxyphenyl ketone gave 5-chloro-2-*n*-pentylphenol which on nitration in acetic acid solution gave a mixture of two mononitrophenols separable by fractional distillation. In an attempted Skraup reaction with the amine obtained by reduction of the lower boiling nitrophenol there was high recovery of

[1] Part IV, Woodcock, *J.*, 1955, 4391.
[2] Byrde and Woodcock, *Ann. Appl. Biol.*, in the press.
[3] Ferguson, *Proc. Roy. Soc.*, 1939, *B*, **127**, 387.
[4] Byrde and Woodcock, *Nature*, 1957, **179**, 539.
[5] Blatt, *Org. Reactions*, Vol. I, p. 342.

unchanged amine, whilst similar treatment of the amine from the second nitration product gave 8-chloro-6-hydroxy-5-*n*-pentylquinoline, which was reduced to the required 6-hydroxy-5-*n*-pentylquinoline by hydrogen in the presence of palladised charcoal.

In order to examine the effect of halogen substitution on fungistatic activity, 7-chloro-8-hydroxy-5-*n*-pentylquinoline was prepared by a similar route from *o*-chlorophenyl valerate.

When tested against the mycelium of *A. niger*, 6-hydroxy-5-*n*-pentylquinoline was considerably less toxic than 8-hydroxy-5-*n*-pentylquinoline; introduction of a nuclear chlorine atom had little effect on the toxicity of the latter hydroxyquinoline. It is hoped that full discussion of the biological results will be published elsewhere.[2]

## Experimental

*Butyl 4-Chloro-2-hydroxyphenyl Ketone.*—*m*-Chlorophenyl valerate [38·4 g.; prepared by heating *m*-chlorophenol (21 g.) with *n*-valeryl chloride (20 ml.) until the evolution of hydrogen chloride ceased] was stirred at 165° during gradual addition of anhydrous aluminium chloride (28 g.) and then heated for a further 1 hr. After addition of ice-cold hydrochloric acid, the product was extracted with ether, the ethereal solution washed with dilute hydrochloric acid and dried ($Na_2SO_4$), and the solvent removed. Distillation of the residue gave unchanged ester (5 g.) and two fractions, b. p. 160—164°/12 mm. (19 g.) (Found: C, 62·0; H, 6·0. $C_{11}H_{13}O_2Cl$ requires C, 62·1; H, 6·1%), and b. p. 190—192°/2 mm. (5 g.). The yield of the lower-boiling fraction, which is the required *ketone* was considerably reduced by a lower temperature in the Fries migration. The lower-boiling fraction (1 g.) was refluxed in acetone (20 ml.) for 4 hr. with powdered potassium permanganate (7 g., added in two portions). After decolorisation with sulphur dioxide, acidic material was isolated from an ethereal extract by using sodium hydrogen carbonate. It crystallised from aqueous methyl alcohol in needles, m. p. 212—213° undepressed by admixture with an authentic specimen of 4-chloro-2-hydroxybenzoic acid.[6] Similar oxidation of the higher-boiling fraction gave 2-chloro-4-hydroxybenzoic acid, m. p. 158—159°, identical with an authentic specimen.[7]

*Nitration of 5-Chloro-2-n-pentylphenol.*—A solution of the above phenol (46 g.) in acetic acid (92 ml.) was stirred at 0—5° during the dropwise addition of 33% v/v nitric acid (31·5 ml.). After a further hour's stirring, water (150 ml.) was added and the whole extracted with ether, washed with water and sodium hydrogen carbonate solution, and dried ($Na_2SO_4$). Removal of the solvent and distillation gave fractions (A) (20 g.), b. p. 145—146°/0·5 mm., and (B) (22 g.), b. p. 200—202°/0·5 mm. [Found (A): C, 54·1; H, 6·2; N, 5·7. Found (B): C, 53·9; H, 6·0; N, 5·7. $C_{11}H_{14}O_3NCl$ requires C, 54·2; H, 5·75; N, 5·75%].

*2-Amino-3-chloro-6-n-pentylphenol.*—The product (A) above (23·5 g.) was shaken in tetrahydrofuran (50 ml.) and with Raney nickel in hydrogen until uptake ceased. After removal of the catalyst on a centrifuge, the solvent was distilled off and the residue triturated with light petroleum (b. p. 40—60°). The solid *product* (8·9 g.) crystallised from light petroleum (b. p. 60—80°) in prismatic plates, m. p. 84—85° (Found: C, 62·0; H, 7·4; N, 6·8. $C_{11}H_{16}ONCl$ requires C, 61·8; H, 7·5; N, 6·55%). An attempted Skraup reaction with this amine as described below gave a product which crystallised from ethyl alcohol–ether in prisms, m. p. 211—212°, undepressed by admixture with 2-amino-3-chloro-6-*n*-pentylphenol hydrochloride, m. p. 212—213°.

*4-Amino-5-chloro-2-n-pentylphenol.*—The nitration product (B) was reduced as described above for product (A). The *amine* crystallised from aqueous methyl alcohol in plates, m. p. 149—150° (Found: C, 62·2; H, 7·4; N, 6·8%).

*8-Chloro-6-hydroxy-5-n-pentylquinoline.*—4-Amino-5-chloro-2-*n*-pentylphenol (8·6 g.), concentrated sulphuric acid (9·6 ml.), and glycerol (8 ml.) were mixed and heated at 165° for 0·5 hr., then arsenic pentoxide (8·6 g.) was added and heating continued for a further 4 hr. The cooled mixture was diluted with water, excess of 10% aqueous sodium hydroxide added, the whole filtered, and the filtrate acidified with acetic acid. The product was extracted with ether, and the ethereal solution washed with water and sodium hydrogen carbonate solution and dried ($Na_2SO_4$). After removal of the solvent the residue separated from aqueous methyl

[6] Sheehan, *J. Amer. Chem. Soc.*, 1948, **70**, 1665.
[7] Hodgson and Jenkinson, *J.*, 1927, 1740.

alcohol and finally from ether–light petroleum (b. p. 40—60°) as a microcrystalline powder (1·4 g.), m. p. 124° (Found: C, 67·0; H, 6·7; N, 5·8. $C_{14}H_{16}ONCl$ requires C, 67·3; H, 6·4; N, 5·6%). The *hydrochloride*, prepared by treating an ethereal solution of the base with dry hydrogen chloride, crystallised from ethyl alcohol–ether in prisms, m. p. 205—206° (Found: C, 58·9; H, 5·8; N, 5·1. $C_{14}H_{17}ONCl_2$ requires C, 58·75; H, 5·9; N, 4·9%).

6-*Hydroxy*-5-n-*pentylquinoline*.—8-Chloro-6-hydroxy-5-*n*-pentylquinoline (1·2 g.) was shaken in a solution of sodium hydroxide (0·24 g.) in water (5 ml.), and for 4 hr. at 100—120° with palladised charcoal (0·6 g.) under hydrogen at 6 atm. On cooling, the filtered solution was acidified with acetic acid, extracted with ether, washed with water, and dried ($Na_2SO_4$). Treatment of this dry ethereal solution with hydrogen chloride gave the *hydrochloride* which separated from ethyl alcohol–ether as a buff-coloured powder (0·4 g.), m. p. 272—274° (Found: C, 66·9; H, 7·2; N, 5·9. $C_{14}H_{18}ONCl$ requires C, 66·8; H, 7·2; N, 5·6%). This hydrochloride was dissolved in a slight excess of dilute sodium hydroxide and acidified with acetic acid, and the *base* extracted with ether. It crystallised from ether–light petroleum (b. p. 60—80°) in prisms, m. p. 124—125° (Found: C, 77·7; H, 8·2; N, 6·4. $C_{14}H_{17}ON$ requires C, 78·1; H, 7·9; N, 6·5%).

*Butyl* 3-*Chloro*-4-*hydroxyphenyl Ketone*.—*o*-Chlorophenyl valerate (26·6 g.) was stirred at 110° during gradual addition of finely powdered aluminium chloride (30 g.) and for a further 2 hr. Isolation of the product as in the previous Fries reaction gave fractions, b. p. 118—120°/10 mm. (5·3 g.) and b. p. 180—184°/4 mm. (18·7 g.). Crystallisation of the latter from ether–light petroleum (b. p. 40—60°) gave rhombic plates, m. p. 97—98° (Found: C, 62·2; H, 6·2. Calc. for $C_{11}H_{13}O_2Cl$: C, 62·1; H, 6·1%). Nguyen-Hoán and Buu-Hoï [8] give m. p. 97°.

2-*Chloro*-5-n-*pentylphenol*.—The above ketone (25 g.) was reduced with amalgamated zinc and hydrochloric acid. The product (18·3 g.), isolated as previously described, had b. p. 138—140°/15 mm. (Found: C, 66·3; H, 7·5. Calc. for $C_{11}H_{15}OCl$: C, 66·5; H, 7·55%). Klarman, Shternov, and Gates,[9] who prepared this compound by chlorination of 4-*n*-pentylphenol with sulphuryl chloride, give b. p. 115—116°/2 mm.

2-*Chloro*-6-*nitro*-4-n-*pentylphenol*.—A solution of the preceding phenol (18·3 g.) in acetic acid (37 ml.) was nitrated as described for the isomeric compound. Distillation of the *product* gave a pale yellow liquid (16·8 g.), b. p. 165—170°/6 mm. (Found: C, 54·5; H, 6·2; N, 5·7. $C_{11}H_{14}O_3NCl$ requires C, 54·2; H, 5·75; N, 5·75%).

2-*Amino*-6-*chloro*-4-n-*pentylphenol*.—Reduction of the corresponding nitrophenol as described for the isomer gave a colourless *amine* (10 g.), b. p. 140—150°/2 mm. Crystallisation from ether–light petroleum (b. p. 40—60°) gave plates, m. p. 57—58° (Found: C, 62·1; H, 7·7; N, 6·7. $C_{11}H_{16}ONCl$ requires C, 61·8; H, 7·5; N, 6·55%).

7-*Chloro*-8-*hydroxy*-5-n-*pentylquinoline*.—The preceding amine (4·3 g.), sulphuric acid (4·8 ml.; *d* 1·84), and glycerol (4 ml.) were heated at 160° for 0·5 hr. and then for a further 4 hr. after addition of arsenic pentoxide (4·3 g.). On cooling, water was added and the *product* isolated by continuous extraction with chloroform. It crystallised from aqueous methyl alcohol in pale yellow monoclinic prisms (0·5 g.), m. p. 107—107·5° (Found: C, 67·4; H, 6·5; N, 5·8. $C_{14}H_{16}ONCl$ requires C, 67·3; H, 6·4; N, 5·6%).

The authors thank Professor W. Baker, F.R.S., for making available the pressure reductor and Mr. D. R. Clifford for the microanalyses.

Department of Agriculture and Horticulture, University of Bristol, Research Station, Long Ashton, Bristol. [*Received, September 17th*, 1957.]

[8] Nguyen-Hoán and Buu-Hoï, *Compt. rend.*, 1947, **224**, 1363.
[9] Klarman, Shternov, and Gates, *J. Amer. Chem. Soc.*, 1933, **55**, 2576.

## 133. *Photochemical Transformations. Part III.* The Constitution of a Steroid Irradiation Product.*

By D. H. R. Barton and A. S. Kende.

The chromophoric system of photodehydroergosterol has been shown to be a *cyclo*propane ring in conjugation with two ethylenic linkages. Hydrogenation affords tetrahydrophotodehydroergosterol which contains a vinyl-*cyclo*propane residue. The relationship between the latter and the secondary hydroxyl group has been defined rigidly. On the basis of these and other observations a constitution has been proposed for photodehydroergosterol.

Although much attention has been devoted to the photochemical transformations of ergosterol, only preliminary work by Windaus and his collaborators [1,2] has been recorded on the effect of ultraviolet light on the triene system of dehydroergosterol (I; R = H). We have confirmed the observation [1,2] that irradiation of its acetate (I; R = Ac) affords in satisfactory yield a crystalline isomer, photodehydroergosteryl acetate. The experiments summarised in the sequel lead us to assign the constitution (V; R = Ac) to this compound.

The earlier workers [1,2] had made the following pertinent observations. Photodehydroergosterol showed a high-intensity absorption maximum at 260 mμ. Its acetate, in contrast to the starting material (I; R = Ac), did not react with maleic anhydride. On hydrogenation in ethanol over platinum it gave tetrahydrophotodehydroergosteryl acetate, the side-chain and one of the nuclear ethylenic linkages being saturated. Hydrogenation over platinum in acetic acid furnished a non-crystalline product with uptake of four mols. of hydrogen.

We began our investigation with the knowledge that the absorption spectrum of the photo-compound acetate [$\lambda_{max.}$ 260 mμ (ε 11,300)] was very similar to that of "ergostatetraene" [3] (IV) which shows $\lambda_{max.}$ 261 mμ (ε 17,600). The conjugation between two ethylenic linkages and a *cyclo*propane ring suggested by this observation was confirmed by the spectrum of the tetrahydro-acetate. This had a broad maximum at 222 mμ (ε 6800) typical [4] of conjugated vinyl*cyclo*propanes.

We first excluded the possibility that the methyl group at position 10 was involved in the formation of a *cyclo*propane ring. Thus tetrahydrophotodehydroergosterol acetate gave no indication (in $CCl_4$) of the infrared band characteristic [5] of $CH_2$ in a *cyclo*propane ring. Also photodehydroergosterol afforded 3·8 *C*-Me groups on Kuhn–Roth oxidation. A simultaneous determination on 5 : 6-dihydroergosterol indicated 3·7 *C*-Me groups. These figures imply that the same number of *C*-Me groups must be present in both compounds.

There are three obvious formulæ, (II), (III), and (V; R = H), consistent with the spectroscopic data. Formula (II) could be excluded easily since oxidation of photodehydroergosterol with chromium trioxide in pyridine afforded a crystalline ketone (VI). This showed a carbonyl band at 1704 cm.$^{-1}$ indicative of a *cyclo*hexanone, not a *cyclo*pentanone as would be required for the ketone from (II).

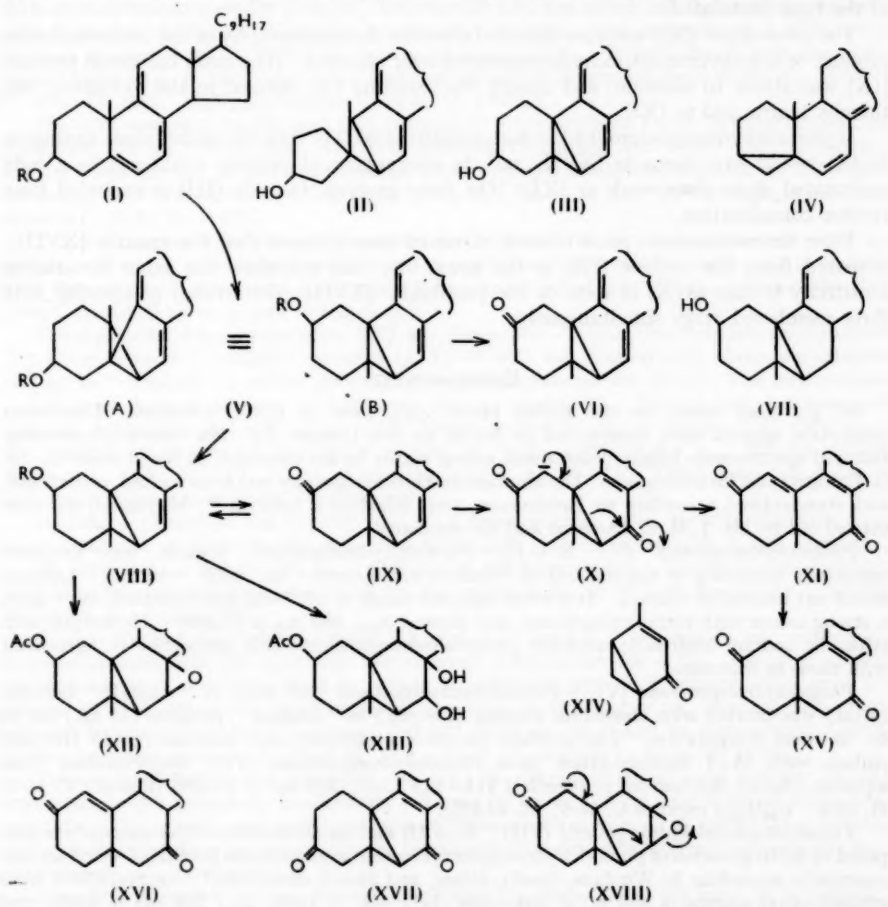
Tetrahydrophotodehydroergosteryl acetate which, as will be shown in the sequel, must be formulated as (VIII; R = Ac), gave a crystalline epoxide (XII) with monoperphthalic acid, and a glycol (XIII) with osmium tetroxide. The latter was stable to ozone, thus confirming the assumption that one of the ethylenic linkages of the compound (I; R = Ac) had been converted into a ring during the photo-reaction. The uptake of 4 mols. of hydrogen on hydrogenation of the photo-product (V; R = Ac) in acetic acid is, of course,

* Part II, *J.*, 1958, 140.

[1] Windaus and Linsert, *Annalen*, 1928, **465**, 148.
[2] Windaus, Gaede, Köser, and Stein, *ibid.*, 1930, **483**, 17.
[3] Fieser, Rosen, and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5397.
[4] *Inter al.*, Zürcher, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1954, **37**, 2145; Rowe, Melera, Arigoni, Jeger, and Ruzicka, *ibid.*, 1957, **40**, 1.
[5] Cole, *J.*, 1954, 3807.

unexceptional if a *cyclo*propane ring be present. Neither the oxide (XII) nor the diol (XIII) showed double-bond absorption in the ultraviolet region, in agreement with the presence of a *cyclo*propane (or other carbon) ring.

Oxidation of tetrahydrophotodehydroergosterol (VIII; R = H) with chromium trioxide in pyridine–benzene gave, as main product, the expected ketone (IX), which exhibited a *cyclo*hexanone band at 1704 cm.$^{-1}$ in agreement with the assigned constitution. Further oxidation of this ketone with the same reagent, followed by chromatography over silica gel, furnished an αβ-unsaturated ketone with an ultraviolet absorption spectrum typical [6] of an umbellulone (as XIV). This is formulated as (X). Its formation suggests (*a*) that the residual ethylenic linkage of tetrahydrophotodehydroergosterol, as implied




by an infrared band at 3030 cm.$^{-1}$ (in $CCl_4$), has at least one vinyl hydrogen atom and (*b*) that the *cyclo*propane ring and the residual ethylenic linkage are in the same six-membered ring. Alternative formulæ such as (VII) for tetrahydrophotodehydroergosterol are thus excluded. The umbellulone (X) showed infrared bands at 1704 (*cyclo*hexanone), 1673 (*cyclo*hexenone), and 1617 (conjugated C=C) cm.$^{-1}$ in agreement with the assigned constitution.

[6] Gillam and West, *J.*, 1945, 98; Eastman, *J. Amer. Chem. Soc.*, 1954, **76**, 4115.

The ketone (X) was extremely sensitive to base, being thereby converted [see (X); arrows] into a diene-dione (XI), which had an intense ultraviolet band at 307 mμ consistent with the chromophore postulated.[7] In the infrared region, this dione (XI) showed bands at **1655** (**1667** in $CCl_4$) (2-*cyclo*hexenones), **1587** and **1563** (conjugated C=C) cm.$^{-1}$ in agreement with the proposed formula. Reduction of it with zinc dust and acetic acid afforded an αβ-unsaturated ketone (XV). The ultraviolet absorption of this compound at **256** mμ implies a heavily substituted enone system and excludes the alternative (XVI) which would absorb at about 240 mμ.[8] Compound (XV) gave infrared maxima at **1702** (*cyclo*hexanone), **1650** (*cyclo*hexenone), and **1595** (conjugated C=C) cm.$^{-1}$ The ready reduction of its precursor (XI) provides chemical evidence [9] that it is a fully conjugated diene-dione of the type postulated.

The diene-dione (XI) was also obtained from the chromatography of the crude oxidation product of tetrahydrophotodehydroergosterol over alumina. The main oxidation product (IX) was stable to alumina, and clearly the diketone (X), formed in the oxidation, was thereby rearranged to (XI).

If photodehydroergosterol had, in fact, constitution (III), then the umbellulone analogous to (X) would have formula (XVII) and its rearrangement product could not be a fully conjugated diene-dione such as (XI). On these grounds formula (III) is excluded from further consideration.

From the mechanistic point of view it was of some interest that the epoxide (XVIII), prepared from the cyclene (IX) in the usual way, did not show the same remarkable sensitivity to base as (X) in spite of the possibility (XVIII; see arrows) of opening both three-membered rings simultaneously.

## Experimental

M. p.s were taken on the Kofler block. $[\alpha]_D$ refer to $CHCl_3$ solutions. Ultraviolet absorption spectra were determined in EtOH on the Unicam S.P. 500 Spectrophotometer. Infrared spectra were kindly determined, unless stated to the contrary, as Nujol mulls by Dr. G. Eglinton and his colleagues. The alumina for chromatography was acid-washed, neutralised, and standardised according to Brockmann and Schodder's method.[10] Microanalyses were carried out by Mr. J. M. L. Cameron and his associates.

*Photodehydroergosterol* (V; R = H).—Photodehydroergosteryl acetate was prepared essentially according to the method of Windaus and Linsert [1] but with "AnalaR" benzene as solvent instead of ethanol. It showed infrared bands at **1727** and **1242** (acetate) cm.$^{-1}$, gave a strong colour with tetranitromethane, and showed $\lambda_{max.}$ **260** mμ (ε 11,300). Hydrolysis with ethanolic sodium hydroxide afforded photodehydroergosterol with properties in agreement with those in literature.

*Photodehydroergosterone* (VI).—Photodehydroergosterol (250 mg.) in "AnalaR" benzene (3 ml.) was treated with chromium trioxide (250 mg.) in "AnalaR" pyridine (12 ml.) for 24 hr. at room temperature. The product, on chromatography over alumina (grade III) and elution with 15 : 1 benzene–ether, gave *photodehydroergosterone* (VI). Recrystallised from aqueous ethanol this had m. p. (needles) 111—113°, $\lambda_{max.}$ 259 mμ (ε 12,500) (Found: C, 85·6; H, 10·4. $C_{28}H_{40}O$ requires C, 85·6; H, 10·3%).

*Tetrahydrophotodehydroergosterol* (VIII; R = H) *and its Derivatives*.—The acetate was prepared by hydrogenation of photodehydroergosteryl acetate over platinum in ethanol–ethyl acetate essentially according to Windaus, Gaede, Köser, and Stein's directions.[3] Recrystallised from ethanol–ethyl acetate it had m. p. 104—105°, $[\alpha]_D$ +8° (*c* 1·90), $\lambda_{max.}$ 222 mμ (ε 6800), and infrared bands at **1733** and **1242** (acetate) cm.$^{-1}$ (Found: C, 81·6; H, 10·9. Calc. for $C_{30}H_{48}O_2$: C, 81·8; H, 11·0%). Hydrolysis with 5% ethanolic sodium hydroxide gave the known tetrahydrophotodehydroergosterol. The alcohol (130 mg.) in "AnalaR" pyridine (3 ml.) was treated with recrystallised toluene-*p*-sulphonyl chloride (170 mg.) for 18 hr. at room temperature.

[7] Cf. Ruzicka, Nisoli, and Jeger, *Helv. Chim. Acta*, 1946, **29**, 2017.
[8] Cf. Dorfman, *Chem. Rev.*, 1953, **53**, 47.
[9] *E.g.*, Dorée, McGhie, and Kurzer, *J.*, 1948, 988; 1949, 570.
[10] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

XUM

Crystallisation from ethanol afforded the *toluene*-p-*sulphonate* (74 mg.), m. p. (needles) 107—108°, $[\alpha]_D$ +31° (*c* 0·36), $\lambda_{max.}$ 224 mμ (ε 16,100) (Found: C, 76·2; H, 9·0. $C_{35}H_{52}O_3S$ requires C, 76·1; H, 9·5%).

Treatment of tetrahydrophotodehydroergosteryl acetate (165 mg.) in " AnalaR " benzene (19·5 ml.) with monoperphthalic acid (105 mg.; by titration) at 0° for 90 min. (uptake of 1·15 mols. of per-acid) gave the corresponding *epoxide*. Recrystallised from aqueous ethanol this (88 mg.) had m. p. (plates) 99—101°, $[\alpha]_D$ −21° (*c* 0·36), no ultraviolet absorption (Found: C, 78·8; H, 10·8. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

*Reaction of Tetrahydrophotodehydroergosteryl Acetate with Osmium Tetroxide.*—Tetrahydrophotodehydroergosteryl acetate (950 mg.) in dry " AnalaR " benzene (5 ml.) was added to osmium tetroxide (1·0 g.) and pyridine (0·1 ml.) in the same solvent (10 ml.) and left in the dark at room temperature for 13 days. Benzene (25 ml.) was added and the solution saturated with hydrogen sulphide. Filtration, evaporation *in vacuo*, and crystallisation from 90% aqueous ethanol (8 ml.) afforded the *triol monoacetate* (XIII). Recrystallised from the same solvent this had m. p. 122°, $[\alpha]_D$ −3° (*c* 6·00), no ultraviolet absorption down to 215 mμ (Found: C, 75·6; H, 10·8. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%).

The triol monoacetate (90 mg.) was refluxed in ethanol (10 ml.) with 4N-aqueous sodium hydroxide (0·5 ml.) for 5 min. The very insoluble crystalline *triol* which was precipitated (73 mg.) was filtered off and recrystallised from *iso*propyl alcohol. It had m. p. 230—235° (decomp.), no ultraviolet absorption (Found: C, 76·6, 76·9; H, 11·3, 11·0. $C_{28}H_{48}O_3,\frac{1}{2}C_3H_8O$ requires C, 76·6; H, 11·2%).

The triol monoacetate (47 mg.) in methylene dichloride (20 ml.) was ozonised at −20° for 20 min. Washing with water, removal of the methylene dichloride *in vacuo*, and hydrolysis with 0·5N-ethanolic potassium hydroxide (5 ml.) under reflux for 20 min. afforded the triol (70%), identified by m. p. and mixed m. p.

*Tetrahydrophotodehydroergosterone* (IX) *and Congeners.*—Tetrahydrophotodehydroergosterol (1·3 g.) in benzene–" AnalaR " pyridine (1 : 1; 10 ml.) was treated with chromium trioxide (1·5 g.) in " AnalaR " pyridine (25 ml.) at room temperature for 18 hr. The oily product (1·2 g.) was chromatographed over alumina (40 g.; grade III). Elution with benzene, and benzene containing 2% of ether, gave *tetrahydrophotodehydroergosterone* (IX) (385 mg.). Recrystallised from ethanol, this had m. p. 116—117°, $[\alpha]_D$ +29° (*c* 1·00), $\lambda_{max.}$ 220 mμ (ε 6500) (Found: C, 84·8; H, 11·7. $C_{28}H_{44}O$ requires C, 84·8; H, 11·2%). This ketone was stable to rechromatography over grade III alumina.

Continued elution of the column with 9 : 1 benzene–ether gave, on crystallisation from ether–methanol or from ethanol, the *diene-dione* (XI) (141 mg., crude), m. p. 189—191°, $[\alpha]_D$ −418° (*c* 0·52), $\lambda_{max.}$ 227 and 307 mμ (ε 6200 and 23,000 respectively). The use of pure pyridine, instead of benzene–pyridine, as solvent for the oxidation led to 37% of the ketone (IX) and 5% of the diene-dione (XI).

Tetrahydrophotodehydroergosterone (50 mg.) in " AnalaR " benzene (6 ml.) containing monoperphthalic acid (40 mg.) was left at room temperature for 4 hr. The product was chromatographed over alumina (5 g.; grade V). Elution with 9 : 1 benzene–ether gave the *epoxide* (XVIII) (18 mg.). Recrystallised from ethanol this had m. p. (needles) 132—134°, infrared bands at 1707 (*cyclo*hexanone) and 853 (epoxide) cm.$^{-1}$ and no high-intensity ultraviolet absorption (Found: C, 81·1; H, 11·4. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·8%).

Tetrahydrophotodehydroergosterone (50 mg.) in dioxan (distilled over sodium; 8 ml.) was treated with potassium borohydride (60 mg.) in water (1·5 ml.) for 1 hr. at room temperature. The product was acetylated with pyridine–acetic anhydride at 55° for 2 hr., to give, on crystallisation from aqueous ethanol, tetrahydrophotodehydroergosteryl acetate (20 mg.) identified by m. p. and mixed m. p.

*Zinc-dust Reduction of the Diene-dione* (XI).—The diene-dione (70 mg.) in " AnalaR " acetic acid (10 ml.) was refluxed with zinc dust (350 mg.) for 45 min. (spectrophotometric control by disappearance of band at 307 mμ). Crystallisation of the product from ethanol gave the *ene-dione* (XV) (21 mg.), m. p. (plates) 198—200°, $[\alpha]_D$ −51° (*c* 0·40), $\lambda_{max.}$ 256 mμ (ε 7900) (Found: C, 81·2; H, 10·5. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·8%).

*Oxidation of Tetrahydrophotodehydroergosterone* (IX) *with Chromium Trioxide in Benzene–Pyridine.*—The ketone (350 mg.) in " AnalaR " benzene (4 ml.) was treated with chromium trioxide (450 mg.) in " AnalaR " pyridine (8 ml.) at room temperature for 20 hr. The solution was poured into ice-water (150 ml.) and kept at 15° whilst being saturated with sulphur dioxide.

Cold 2N-sulphuric acid (100 ml.) was added and the solution extracted with 1 : 1 ether–benzene (3 × 50 ml.). The combined organic extracts were washed successively with 2N-sulphuric acid, water, saturated sodium hydrogen carbonate, and water, then dried ($MgSO_4$), and the solvent removed *in vacuo*. The product was chromatographed over silica gel (B.D.H.; 10 g.). Elution with 7 : 3 and 6 : 4 light petroleum (b. p. 40—60°)–benzene gave unchanged tetrahydrophotodehydroergosterone (58 mg.). Elution with 1 : 2 light petroleum (b. p. 40—60°)–benzene, with benzene and with 30 : 1 benzene–ether furnished the *umbellulone* (X) (70 mg.). Recrystallised from ether–methanol this had m. p. (needles) 163—165°, $[\alpha]_D$ +78° (*c* 0·75), $\lambda_{max.}$ (broad and flat) 225 and 283 mμ (ε 5200 and 3100) (Found: C, 81·7; H, 10·6. $C_{28}H_{42}O_2$ requires C, 81·9; H, 10·3%). This compound (21 mg.) in ethanol (3 ml.) was treated with 5% methanolic sodium hydroxide (2 drops) for 30 sec. 20% Aqueous acetic acid (2 drops) was added. Crystallisation of the product from ether–methanol gave the diene-dione (XI) (15 mg.) identified by m. p., mixed m. p., and ultraviolet absorption spectrum. The spectrum of the diene-dione is seen as soon as an ethanolic solution of the compound (X) s treated with a trace of base. The same spectrum is seen on warming the compound (X) on the steam-bath with 0·2N-ethanolic sulphuric acid.

We thank the Government Grants Committee of the Royal Society and Imperial Chemical Industries Limited for financial assistance and Dr. J. Klein for his valuable help. One of us (A. S. K.) is indebted to the American Cancer Society for a Postdoctoral Fellowship Grant.

THE UNIVERSITY, GLASGOW, W.2.
IMPERIAL COLLEGE, LONDON, S.W.7. [*Received, September 30th*, 1957.]

---

## 134. *Ferrocene Derivatives. Part VII.*[1] *Some Sulphur Derivatives.*

By G. R. KNOX and P. L. PAUSON.

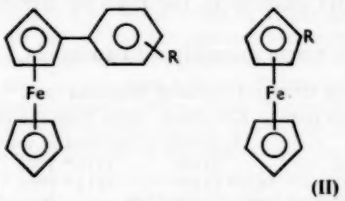
Ferrocenesulphonic acid has been obtained by an improved method and converted *via* the sulphonyl chloride into ferrocenethiol. The latter has been characterised as its *S*-methyl and *S*-allyl ether, as its *S*-carboxymethyl and *S*-acetyl derivative, and as the corresponding disulphide.

AFTER the demonstration by Woodward *et al.*[2] that ferrocene can undergo Friedel–Crafts acylation, numerous studies have amply demonstrated that it behaves as a typical aromatic system towards electrophilic substitution in general. On the one hand, its reactivity has been shown to be comparable with that of highly activated benzene derivatives.[1,3,4] On the other, its reactions are limited by the ease of oxidation of ferrocene to the ferricinium ion, preventing, *e.g.*, direct halogenation or nitration. However, the investigation of directive influences within the five-membered ring still awaits the preparation of suitably substituted ferrocenes, and the present study is intended as a contribution in this direction. Hitherto only the alkylferrocenes have received attention from this point of view. Rosenblum [5] showed that a single ethyl group exerts insufficient activating influence to direct exclusively or even predominantly into the same ring (cf. also Nesmeyanov and Vol'kenau [6]). Recently Rinehart and his collaborators [7] have further shown that 1 : 1′-dimethylferrocene is substituted to roughly equal degree in the 2- and the 3-position in Friedel–Crafts acetylation. The preference for the latter position in the case of 1 : 1′-di*iso*propylferrocene is therefore probably attributable largely to steric hindrance of attack at the 2-position.[7]

If any significant difference in reactivity exists between these positions it should be

[1] Part VI, *J.*, 1958, **656**.
[2] Woodward, Rosenblum, and Whiting, *J. Amer. Chem. Soc.*, 1952, **74**, 3458.
[3] Part V, *J.*, 1958, **650**.
[4] Graham, Lindsey, Parshall, Peterson, and Whitman, *J. Amer. Chem. Soc.*, 1957, **79**, 3416.
[5] Rosenblum, Thesis, Harvard, 1953.
[6] Nesmeyanov and Vol'kenau, *Doklady Akad. Nauk S.S.S.R.*, 1956, **111**, 605.
[7] Rinehart, Motz, and Moon, *J. Amer. Chem. Soc.*, 1957, **79**, 2748.

more apparent when substituents more strongly activating than alkyl are employed. At the beginning of our work aminoferrocene [8,9] was the only known derivative of this type. Unfortunately it appears unsuitable for the study of further substitution owing to its low stability. This is probably due largely to the ease of oxidation and it appears likely that all electron-donating substituents will be found to facilitate oxidation of the




(I) (II)

ferrocene nucleus. A study of the factors influencing such oxidation is in progress. The results already obtained [10] on a group of substituted phenylferrocenes (I) show that groups which activate the benzene ring increase the ease of oxidation.

Methods employed for the introduction of oxygen atoms into benzene nuclei have not hitherto proved applicable to the preparation of hydroxyferrocene. We therefore turned our attention to its sulphur analogue, ferrocenethiol (II; R = SH) which appeared more accessible and also likely to prove more stable than its oxygen analogue. Its preparation has been achieved in three steps from ferrocene, *viz.*, sulphonation, conversion of the resultant monosulphonic acid (II; R = $SO_3H$) into the sulphonyl chloride, and reduction with lithium aluminium hydride.

Sulphonation of ferrocene was first described by Weinmayr,[11] who showed that concomitant oxidation of ferrocene by sulphuric acid can be minimised by employing acetic anhydride as solvent. The main product was the disulphonic acid, but ferrocenemonosulphonic acid could be isolated (as its ammonium salt) when a substantial excess of ferrocene was employed. Nesmeyanov *et al.*[12] reported the use of the pyridine–sulphur trioxide complex for the preparation of the disulphonic acid and more recently also of the monosulphonic acid; [6] no details of their method are available. We found chlorosulphonic (chlorosulphuric) acid in acetic anhydride to be an efficient reagent for preparation of the monosulphonic acid. We isolated the free acid as its stable, crystalline, ether-soluble dihydrate and characterised it as ammonium salt and methyl ester. The disulphonic acid is formed by the same method when two molecular equivalents of chlorosulphonic acid are employed and has been converted into its (previously unknown) dimethyl ester.

Treatment of the monosulphonic acid with phosphorus pentachloride or thionyl chloride causes extensive oxidative decomposition, but phosphorus trichloride affords the sulphonyl chloride. This is reduced to ferrocenethiol in almost quantitative yield by lithium aluminium hydride in ether. The thiol is low-melting and orange-yellow, but has not been obtained completely pure owing to the extreme ease with which it is oxidised to the disulphide. The latter is readily obtained by passing air through an alkaline solution of the crude reduction product. The reverse process could not be effected with aqueous alkaline glucose or arsenious oxide solutions, but has been brought about by reduction again with lithium aluminium hydride. The thiol thus regenerated has been characterised as its crystalline *S*-allyl and *S*-acetyl derivative. Samples obtained directly from the sulphonyl chloride have also been converted into the liquid methylthio-compound (II; R = Me) and to (ferrocenylthio)acetic acid (II; R = $S{\cdot}CH_2{\cdot}CO_2H$).

[9] Nesmeyanov, Perevalova, Golovnya, and Shilovtseva, *Doklady Akad. Nauk S.S.S.R.*, 1955, **102**, 535.
[9] Arimoto and Haven, *J. Amer. Chem. Soc.*, 1955, **77**, 6295.
[10] Broadhead, Thesis, Sheffield, 1956.
[11] Weinmayr, *J. Amer. Chem. Soc.*, 1955, **77**, 3009.
[12] (*a*) Nesmeyanov, Abs. XIVth Internat. Congr. Pure Appl. Chem., Zürich, 1955, p. 193; (*b*) Nesmeyanov and Vol'kenau, *Doklady Akad. Nauk S.S.S.R.*, 1956, **107**, 262.

The disulphide was also isolated (but in variable and generally low yield) on catalytic reduction of the sulphonyl chloride: we did not succeed in isolating the expected sulphinic acid from this reaction. We also failed to obtain diferrocenyl sulphone from an attempted Friedel–Crafts reaction between ferrocenesulphonyl chloride and ferrocene: the only identifiable product, isolated in low yield, was again the disulphide, presumably implying reduction of the sulphonyl chloride to the thiol by ferrocene in presence of aluminium chloride.

The sulphonyl chloride reacts smoothly with ammonia, to yield ferrocenesulphonamide.

*Positions of the strongest infrared maxima (cm.$^{-1}$) below 2000 cm.$^{-1}$.*

(All our measurements refer to KBr discs; those from the literature refer to solutions.)

| Compound | Positions of maxima in wave numbers (cm.$^{-1}$). | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $C_{10}H_9Fe{\cdot}SO_3^-$ $Fe^{++}$ salt | 1656 | — | — | 1190[a] | — | 1112[d] | 1065 | 1031 | 1021 | 1010[d] | 843 | 822 | — | — |
| $NH_4^+$ salt | 1641 | — | 1413[b] | 1180[a] | — | 1112[d] | 1055 | 1030 | 1020 | 1006[d] | 823 | 819 | — | — |
| *p*-$C_6H_4Me{\cdot}SO_3^-NH_4^+$ ... | 1484 | 1448 | 1420 | 1190[a] | 1138 | — | 1044 | 1018 | — | — | 819 | — | 687 | — |
| $C_{10}H_9Fe{\cdot}SO_3Me$ ..... | — | — | 1360 | 1209 | 1159 | 1112[d] | 1039 | 1025 | — | 1006[a] | 988 | 844 | 831 | 771 |
| 1 : 1′-$C_{10}H_8Fe(SO_3Me)_2$ | — | 1465 | 1367 | 1211 | 1158 | — | 1042 | 1030 | — | — | 988 | 878 | 838 | 773 |
| *p*-$C_6H_4Me{\cdot}SO_3Me$ [13] ..... | — | — | 1375 | 1185 | 1100 | — | — | — | — | — | — | — | — | — |
| $C_{10}H_9Fe{\cdot}SO_2Cl$ ..... | — | — | 1377 | 1210 | 1149 | 1116[d] | 1036 | 1020 | — | 1008[d] | 836 | 823 | — | — |
| $Ph{\cdot}SO_2Cl$ [a, 13] ..... | — | — | 1390 | 1185 | 1120 | — | — | — | — | — | — | — | — | — |
| $(C_{10}H_9FeS\cdot)_2$ ..... | — | — | 1411[d] | 1171 | — | 1111 | 1054[d] | 1030 | — | 1005 | 890 | 834 | 821 | 807 |
| $Ph_2S_2$ [13] ..... | — | — | — | 1201 | — | — *ca.* 1070[f] | | — | — | — | — | — | — | — |

[a] Bellamy [14] gives 1366 and 1166 for *p*-$C_6H_4Me{\cdot}SO_2Cl$. [b] Due to $NH_4^+$ (cf., *e.g.*, ref. 14). [c] Broad band; exact location doubtful owing to lack of resolution. [d] Weaker than the other maxima listed. [e] Shoulder. [f] Approx., as judged from published curve.

The infrared spectra of some of the products are collected in the Table and compared with those of corresponding benzene derivatives.[13,14] The bands which have been considered as characteristic of the functional groups show good agreement in the two series. In addition, the ferrocene derivatives which bear a single substituent all possess the bands near 1005 and 1110 cm.$^{-1}$ which have previously been found to be associated with the presence of an unsubstituted *cyclo*pentadiene ring in ferrocene derivatives.[5,15]

## Experimental

M. p.s were determined in evacuated capillaries. Ligroin refers to the solvent of b. p. 60—80°. Alumina was Spence's grade H which had been exposed to air for 6 hr.

*Ferrocenesulphonic Acid.*—Ferrocene (8 g., 0·043 mole) was dissolved in acetic anhydride (60 ml.) at 23° and technical chlorosulphonic (chlorosulphuric) acid (5 g., 0·043 mole) added from a capillary tube to the rapidly stirred solution during 10 min. The solution immediately darkened, hydrogen chloride was evolved, and the temperature rose to 27°. After 24 hr. at room temperature, the solution was filtered (Caution; explosion) into cold water (75 ml.) and the mixture, which had reached 87°, cooled by addition of further ice-water (25 ml.). The precipitated ferrocene (1·1 g., 14%) was filtered off and the filtrate evaporated to dryness. The residue was extracted with ether, yielding *ferrocenesulphonic acid dihydrate* (7·37 g.; 66% based on unrecovered ferrocene), m. p. 88—92°, as brown prisms. Recrystallisation from benzene afforded yellow plates, m. p. 103—104° [Found: C, 39·8; H, 4·6; $H_2O$ (by Karl Fischer titration), 12·7, 11·7, 11·8, 11·3%; equiv. wt., 296. $C_{10}H_{16}O_5SFe,2H_2O$ requires C, 39·7; H, 4·6; $H_2O$, 11·9%; equiv. wt., 302]. The ether-insoluble residue was extracted with absolute methanol, yielding a brown solid (2·5 g.; 30%) for which analysis suggested the constitution $(C_{10}H_9FeSO_3^-)_2Fe^{++},4H_2O$. It thus resembles the product isolated by Weinmayr [11] on disulphonation of ferrocene. This *product* crystallised from methanol or glacial acetic acid as a khaki powder [Found: C, 36·75, 36·3, 36·4; H, 4·3, 4·3, 4·2; $H_2O$ (by Karl Fischer titration), 10·3, 11·0. $C_{20}H_{18}O_6S_2Fe_3,4H_2O$ requires C, 36·5; H, 4·0; $H_2O$, 10·9%]. Addition of concentrated ammonia solution to its methanol solution gave a brown precipitate (presumably a mixture of ferrous and ferric hydroxide) and, on evaporation of the filtrate, the ammonium salt of ferrocenesulphonic acid crystallised as yellow plates. After being dried in a vacuum desiccator ($CaCl_2$) for 24 hr. this was a monohydrate (Found: C, 39·5; H, 5·2. Calc. for $C_{10}H_{15}O_4NSFe$: C, 39·7; H, 5·0%).

[13] Schreiber, *Analyt. Chem.*, 1949, **21**, 1168.
[14] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen & Co., Ltd., London, 1954.
[15] Part I, *J. Amer. Chem. Soc.*, 1954, **76**, 2187.

*Methyl Ferrocenesulphonate.*—Ethereal diazomethane [from *N*-nitrosomethylurea (1 g.)] was added to a solution of the sulphonic acid (0·1 g.) in ether (10 ml.). After the evolution of nitrogen had ceased, the solvent was evaporated, leaving *methyl ferrocenesulphonate* as an orange oil (90 mg., 95%) which crystallised from ligroin as yellow rods, m. p. 54—55° (Found: C, 47·3; H, 4·4. $C_{11}H_{12}O_3SFe$ requires C, 47·2; H, 4·3%).

*Disulphonation.*—Chlorosulphonic acid (5·8 g., 0·05 mole) was added dropwise in 3 min. to a rapidly stirred solution of ferrocene (4·6 g., 0·025 mole) in acetic anhydride (75 ml.), causing the temperature to rise from 25° to 40°. After the mixture had been stirred for 16 hr. and set aside for a further 6 hr. the precipitated ferrocenedisulphonic acid was filtered off and washed with acetic anhydride (15 ml.). It was converted into the diammonium salt (5·0 g., 52·6%) by dissolution in concentrated aqueous ammonia, evaporation to dryness, and crystallisation from ethanol–benzene. The acetic anhydride mother-liquors, worked up as described above, yielded the monosulphonic acid (0·8 g., 10·6%) and its ferrous salt (1·75 g., 32%).

The free disulphonic acid is extremely hygroscopic and rapidly becomes blue on exposure to air; but it has been stored under anhydrous ether for several months without decomposition. *Dimethyl ferrocene-1 : 1′-disulphonate* was prepared like the above monosulphonic ester, from an ether suspension of the disulphonic acid and excess of diazomethane. It crystallised from ether as golden-yellow plates, m. p. 142—143° (Found: C, 38·1; H, 4·1. $C_{12}H_{14}O_6S_2Fe$ requires C, 38·4; H, 4·0%).

*Ferrocenesulphonyl chloride.*—Crude ferrocenesulphonic acid (62 g., 0·2 mole) was added in portions to phosphorus trichloride (210 ml., 2·4 moles), preheated to 50°, at such a rate as to maintain gentle refluxing. The mixture was then heated on a water-bath until evolution of hydrogen chloride ceased (approx. 6 hr.), diluted with boiling ligroin (50 ml.), and filtered. The orange filtrate was evaporated under reduced pressure and the residual solid (50 g.) crystallised from ligroin, giving *ferrocenesulphonyl chloride* (48·1 g., 82%) as crimson needles, m. p. 100°, which darkened rapidly in moist air (Found: C, 42·6; H, 3·4. $C_{10}H_9O_2SClFe$ requires C, 42·2; H, 3·2%).

*Ferrocenethiol and Diferrocenyl Disulphide.*—To a stirred solution of lithium aluminium hydride (3·8 g., 0·1 mole) in ether (150 ml.) under nitrogen, the sulphonyl chloride (7·11 g., 0·025 mole) in the same solvent (100 ml.) was added during 35 min. After 18 hours' refluxing, ethyl acetate (5 ml.) was added dropwise, followed by wet ether (50 ml.) and then 3·5N-sulphuric acid (300 ml.). The ether layer was separated, dried, and evaporated, yielding ferrocenethiol as a foul-smelling oil, b. p. 110°/0·005 mm., which at −70° formed orange crystals.

A stream of air was passed for 18 hr. through a solution of the crude thiol in ethanol (100 ml.), water (250 ml.), and ammonia (100 ml.; *d* 0·88). During this period *diferrocenyl disulphide* (5·21 g., 96%) was precipitated as a pale yellow powder, m. p. 188°. Chromatography on alumina and crystallisation from benzene afforded golden-yellow plates, m. p. 192° (Found: C, 55·1; H, 4·0. $C_{20}H_{18}S_2Fe_2$ requires C, 55·35; H, 4·2%). In only one of several such experiments chromatography yielded a small by-product of unknown structure. This crystallised from ligroin as yellow plates, m. p. 54° (Found: C, 57·2; H, 5·6%).

The disulphide was reduced back to the thiol by lithium aluminium hydride, by the method described above except that the reflux period was 1·5 hr. and tetrahydrofuran was used to dissolve the disulphide.

*Catalytic Hydrogenation of the Sulphonyl Chloride.*—This was attempted with 10% palladium–charcoal and ether. Both the rate of hydrogen uptake and the yields of products were very variable. The only products isolated after extraction with water and chromatography of the residue from evaporation of the ether layer were the sulphonic acid from the aqueous extract and the disulphide from the chromatogram.

*Ferrocenyl Thiolacetate* (II; R = S·COMe).—To crude ferrocenethiol, prepared from the disulphide (1·08 g., 0·0025 mole), acetyl chloride (7 ml., 0·1 mole) was added and the mixture heated on a water-bath for 1 hr., then kept overnight. Water (100 ml.) was added, the mixture extracted with ether, and the ether layer washed with sodium hydrogen carbonate solution and with water, and dried ($Na_2SO_4$). Removal of the ether left a brown oil (0·7 g.) which yielded yellow needles of *ferrocenyl thiolacetate*, m. p. 56—57° (from ligroin at −78°) (Found: C, 55·6; H, 4·7. $C_{12}H_{12}OSFe$ requires C, 55·4; H, 4·65%). Diferrocenyl disulphide (0·35 g., 32% recovery) was obtained by chloroform-extraction of the aqueous suspension remaining after the above ether extraction.

*Methylthioferrocene.*—To crude thiol, prepared from the sulphonyl chloride (7·11 g.), sodium

hydroxide (4 g., 0·1 mole) in deaerated water (50 ml.) was added. Cooling of the resultant solution caused the separation of the sodium salt of the thiol as yellow crystals. Freshly distilled dimethyl sulphate (3·15 g., 0·025 mole) was added in three portions, in an atmosphere of nitrogen, stoppered, and shaken for 15 min. after each addition. The mixture was finally warmed to 60° for a further 15 min., cooled, and extracted with chloroform (4 × 50 ml.). On being washed with water, dried, and evaporated, the extract afforded a red oil (5·9 g.) which was chromatographed in ligroin on alumina. The main band yielded the *sulphide* (5·17 g., 89%) followed by some of the disulphide (0·45 g., 8%) which was eluted with benzene. Methylthioferrocene was obtained as an unpleasant-smelling orange-red liquid, b. p. 97·5—98°/0·1 mm., $n_D^{25}$ 1·6488 (Found: C, 56·9; H, 5·2. $C_{11}H_{12}SFe$ requires C, 56·9; H, 5·2%). No methylation took place when a solution of the thiol in ether was treated with excess of diazomethane: only the disulphide was recovered on chromatography of the product.

*Allylthioferrocene.*—The thiol, prepared from the disulphide (1·085 g., 0·0025 mole), was converted into its sodium salt by sodium hydroxide (0·2 g., 0·005 mole) in water (5 ml.). A solution of allyl bromide (1·2 g.; 0·01 mole) in acetone (50 ml.) was added, causing immediate dissolution of the sodium salt. The mixture was then refluxed for 5·5 hr., the solvent removed under reduced pressure, and the orange residue dissolved in chloroform. The dried chloroform solution was evaporated *in vacuo* and the residue chromatographed in ligroin on alumina. Ligroin eluted the *allylthio-derivative* (0·4 g., 65% based on unrecovered disulphide) which crystallised, on cooling of the concentrated ligroin solution to −70°, as yellow rods, m. p. 32° (Found: C, 60·25; H, 5·7. $C_{13}H_{14}SFe$ requires C, 60·5; H, 5·5%). Benzene eluted unchanged disulphide (0·56 g., 52%) from the chromatogram.

*(Ferrocenylthio)acetic acid.*—The crude thiol [from the sulphonyl chloride (2·6 g.; 0·009 mole)] was mixed with potassium hydroxide (0·28 g.), anhydrous potassium carbonate (2·8 g.), chloroacetic acid (0·86 g., 0·009 mole), and acetone (50 ml.). The mixture was refluxed for 3 hr., left overnight, and then evaporated and the residue dissolved in warm (60°) aqueous potassium hydroxide (5 g. in 50 ml.). The solution was aerated for 18 hr., the precipitated disulphide (0·93 g., 47%) filtered off, and the filtrate acidified with dilute hydrochloric acid and extracted with ether (4 × 30 ml.). The extracts were dried ($Na_2SO_4$) and evaporated under reduced pressure, and the residue crystallised from ligroin containing a little benzene. *(Ferrocenylthio)acetic acid* (1·06 g., 42%) formed orange-yellow rods, m. p. 110·5°, and was slightly hygroscopic (Found: C, 52·0; H, 4·4. $C_{12}H_{12}O_2SFe$ requires C, 52·2; H, 4·4%).

*Ferrocenesulphonamide.*—A solution of ferrocenesulphonyl chloride (1·42 g., 0·005 mole) and ammonia (20 ml.; *d* 0·88) in acetone (20 ml.) was heated on a steam-bath for 1 hr. Most of the solvent was removed by distillation, and water (20 ml.) added. The precipitate was filtered off, washed with water (20 ml.), and recrystallised from ethanol, yielding yellow-brown prisms of *ferrocenesulphonamide* (1 g., 75%), m. p. 175° (Found: C, 45·0; H, 4·5. $C_{10}H_{11}O_2NSFe$ requires C, 45·3; H, 4·2%).

*Attempted Friedel–Crafts Reaction between Ferrocene and Ferrocenesulphonyl Chloride.*—To a stirred mixture of the sulphonyl chloride (1·74 g., 0·006 mole) and ferrocene (0·57 g., 0·003 mole) in dry, alcohol-free chloroform (75 ml.) under nitrogen at 0°, anhydrous aluminium chloride (1·63 g., 0·024 mole) was added. The mixture was stirred for 16 hr. during which the temperature was allowed to rise gradually (to 23°). Ice (100 g.), concentrated hydrochloric acid (3 ml.), and a little titanous chloride solution were then added. The organic layer was separated, washed, and dried and the chloroform removed *in vacuo*. The residual orange solid (0·675 g.) was chromatographed on alumina (50 g.) with ligroin as solvent. Unchanged ferrocene (0·43 g., 76%) was followed by a band, which on elution with benzene afforded diferrocenyl disulphide (115 mg.), identified by m. p., mixed m. p., and infrared spectrum (Found: C, 55·3; H, 4·3%). A minute amount of a third, unidentified substance was eluted from the column in one of two such experiments and, crystallised from ligroin, had m. p. 65° (Found: C, 48·1; H, 5·4%).

The authors thank Dr. M. Hunt, of E.I. du Pont de Nemours & Co., for generous gifts of ferrocene, and the Department of Scientific and Industrial Research for a maintenance grant (to G. R. K.).

THE UNIVERSITY, SHEFFIELD, 10. [*Received, October 11th*, 1957.]

## 135. *Physicochemical Studies on Starches. Part IX.* The Mechanism of the β-Amylolysis of Amylose and the Nature of the β-Limit Dextrin.*

By J. M. G. Cowie, I. D. Fleming, C. T. Greenwood, and D. J. Manners.

The mechanism of the hydrolysis of amylose by (*a*) pure β-amylase, and (*b*) β-amylase and Z-enzyme, has been studied by measuring the $\overline{D.P.}$ of the residual polymer at varying degrees of conversion into maltose. Amylose fractionated severally in presence and absence of air, and a sub-fraction obtained by aqueous leaching of the granule, have been used as substrates. The molecular properties of the various 50% conversion dextrins and the 77% β-limit dextrins were examined in detail. In all cases, hydrolysis proceeded by an essentially single-chain mechanism as there was no evidence of molecules other than amylose of $\overline{D.P.} \geqslant$ the original and maltose in the digest. The structure of the β-limit dextrin, which is thought to contain a randomly-situated barrier to β-amylolysis, is discussed.

The action of β-amylase on amylose, which commences at the non-reducing end of the molecule, involves hydrolysis of alternate α-1 : 4-glucosidic linkages with the production of maltose. In a recent paper,[1] we reported the β-amylolysis of an amylose of high molecular weight, prepared [2] by thymol fractionation of potato starch after complete disruption of the granules. Our results confirm that the *pure* enzyme degrades only *ca.* 75% of amylose, and that for complete conversion into maltose a second enzyme (Z-enzyme) is required. The specificity of the latter enzyme was examined, and evidence presented that the β-amylolysis limit for the pure amylose is not an artefact associated with the colloidal instability of the amylose substrate.[1] The nature of the barrier to β-amylolysis is not known.

The specific mode of action of the β-amylase has been in dispute.[3] Maltose may be produced by the enzyme either by (1) attachment to one amylose molecule and then, by stepwise removal of maltose units, complete degradation before attack on another amylose molecule (" single-chain " action), or (2) by removal of one maltose unit on each random collision with an amylose molecule, with the result that all chains in the system will be shortened simultaneously (" multi-chain " action). Reaction mechanisms between (1) and (2) are also possible. However, determination of the molecular weight of the residual polysaccharide at intermediate stages of β-amylolysis will indicate which mechanism is operative. Under normal experimental conditions, with a large substrate : enzyme ratio, the number-average degree of polymerisation ($\overline{D.P.}$) of the residual amylose at any time during a single-chain reaction will be the same as that for the original up to the stage when the number of substrate molecules is approximately equal to the number of enzyme molecules (at this point, a multi-chain mechanism is inevitable). For multi-chain action throughout, the $\overline{D.P.}$ of the amylose will decrease as the reaction proceeds, the reduction being proportional to the percentage conversion into maltose. Experiments of this type have been carried out by Kerr and Cleveland,[4] who found that the polymeric product isolated at about 50% conversion into maltose possessed virtually the same iodine affinity, limiting viscosity number, and $\overline{D.P.}$ as the original amylose. In our work (a preliminary account of which has appeared [5]), we have extended this type of experiment to include the measurement of the $\overline{D.P.}$ of the residual polymer at varying degrees of conversion into

* Part VIII, *J.*, 1957, 4640.

[1] Cowie, Fleming, Greenwood, and Manners, *J.*, 1957, 4430.
[2] Cowie and Greenwood, *J.*, 1957, 2862.
[3] See Greenwood, *Adv. Carbohydrate Chem.*, 1956, **11**, 335.
[4] Kerr and Cleveland, *J. Amer. Chem. Soc.*, 1951, **73**, 2421.
[5] Cowie, Fleming, Greenwood, and Manners, *Chem. and Ind.*, 1957, 634.

maltose resulting from the action of (*a*) pure β-amylase, and (*b*) β-amylase and Z-enzyme. Amylose fractionated severally in presence and absence of air, and a subfraction obtained by aqueous leaching of the granule, have been used as substrates. The molecular size of various 50% conversion dextrins and 77% β-limit dextrins has been examined, and the structure of the β-limit dextrin is discussed.

## Experimental

*Preparation of Amylose Samples and their Characterisation.*—Potato starch (var. Arran Banner) was fractionated by (1) dispersion in the presence or absence of oxygen, and (2) aqueous leaching at 70°. These methods and those used to characterise the polymers have been described in detail previously in this Series.

*Preparation of Enzymes.*—Barley β-amylase and soya-bean β-amylase were used. Their preparation and properties have been described elsewhere.[1]

*Digest Conditions.*—At pH 4·6 and 35° soya-bean β-amylase showed no Z-enzyme activity and converted 77% of amylose samples of high $\overline{D.P.}$ into maltose, whilst under these conditions barley β-amylase hydrolysed all samples completely.[1] Amylose was dissolved directly in water from the well-centrifuged butan-1-ol complex and buffered with acetate to pH 4·6. Enzyme solution [1] was added and the reaction rate followed by withdrawal of aliquot parts at intervals and estimations of the liberated maltose. In all digests, the concentration of enzyme (100 units per mg. of amylose) was such that 50% conversion had occurred within 30 min., and hence retrogradation of amylose was unlikely.

*Isolation of and Measurements on β-Amylolysis Products.*—The $\overline{D.P.}$ of the polymeric product at different percentage conversions was obtained by withdrawing aliquot parts (2 ml.) of the digest and adding M-potassium hydroxide (0·5 ml.). The resultant 0·2M-potassium hydroxide solution (maximum concentration of amylose, 0·18 g./100 ml.) was examined directly in the Spinco ultracentrifuge. Each aliquot portion was studied at three dilutions; the limiting dilution was 0·02 g./100 ml. The 50% conversion and 77% β-limit dextrins were isolated by adding butan-1-ol, then heating the digest for 2 min. on a boiling-water bath (to complete deactivation of enzyme) and allowing the butan-1-ol complexes to be precipitated at room temperature during 24 hr. After removal by centrifugation, the complexes were thoroughly washed with butan-1-ol-saturated water to remove maltose.

## Discussion

A study of the β-amylolysis of amylose is complicated by the fact that the β-limit depends on the method of preparation of the amylose. Our aqueous leaching experiments [1,2,6] have shown that potato starch granules contain an easily accessible amylose fraction of relatively low molecular weight, which is completely hydrolysed by pure β-amylase. In this work, the action pattern of β-amylase on the *whole* amylose has been studied in order to investigate the β-limit dextrin and also to use conditions equivalent to those of other workers. The action pattern under these conditions proved to be identical with that for the completely linear amylose prepared by aqueous leaching.

*Action of Pure β-Amylase.*—(a) *Whole amylose.* Preliminary trial digests showed that the sample of amylose used ($\overline{D.P.}$ 3200) gave 77% conversion into maltose. When aliquot parts were removed at intervals, and studied in the ultracentrifuge, the sedimentation constant ($S_{20}$) of the residual polymer as a function of the concentration ($c$) was as shown in Fig. 1*a*. (The sedimentation constant for amylose is concentration-dependent, as previously reported.[7]) All the points lie on the same curve, within experimental error, although there is a tendency for the values in the earlier stages of conversion to be slightly higher. Fig. 1*a* also shows the corresponding plot of $S_{20}$ against $S_{20}.c$ as recommended by Gralén [8] to facilitate extrapolation to infinite dilution. The points again lie on the same curve. The limiting value of $S_{20}$ for all the residual amyloses was therefore independent of the degree of conversion into maltose up to and including the 77% limit. This result would not be expected on the basis of multi-chain action.

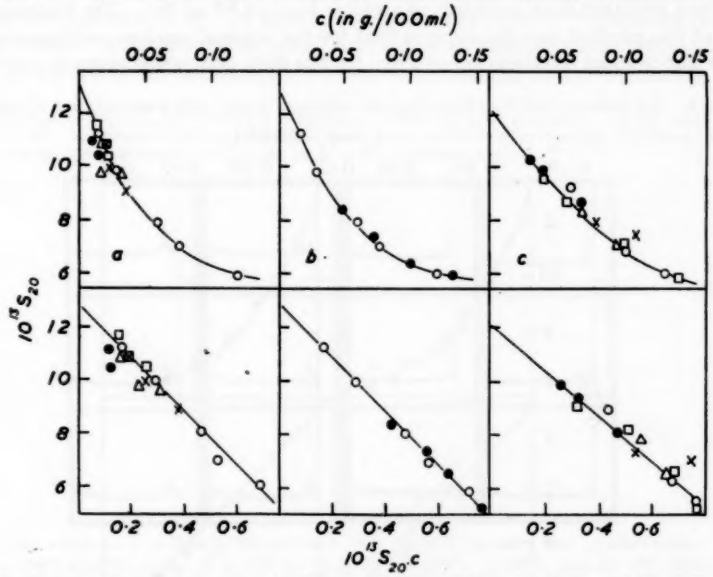
[6] Cowie and Greenwood, *J.*, 1957, 4640.
[7] Bryce, Cowie, and Greenwood, *J. Polymer. Sci.*, 1957, **25**, 251.
[8] Gralén, Inaugural Diss., Uppsala, 1944.

In order to confirm that the sedimentation constant of the β-limit dextrin was unchanged, it was isolated from a large-scale digest. A comparison of the properties with those for the original amylose were as shown:

| | $[\eta]$ | Iodine affinity | $10^{13}(S_{20})_0$ |
|---|---|---|---|
| Original amylose ..... | 430 | 19·5 | 13·1 |
| 77% limit ..... | 415 | 19·2 | 13·1 |

The sedimentation results are shown in Fig. 1*b*. The agreement in sedimentation constants shows that the liberated maltose does not influence $S_{20}$ when portions of the digest are studied directly. The properties of the two polymers are identical within experimental error.

FIG. 1. $S_{20}$ versus $c$ *and* $S_{20}$ versus $S_{20}.c$ *for amyloses treated with pure β-amylase.*




(*a*) *Effect of enzymic hydrolysis*: ○ *original amylose*; × 35% *conversion*; △ 45% *conversion*; □ 55% *conversion*; ● 77% *conversion into maltose.*
(*b*) *Original amylose* ○ *and* 77% *limit dextrin* ●.
(*c*) *Effect of enzymic hydrolysis (oxygen-treated amylose)*: ○ *original amylose*; × 23% *conversion*; △ 34% *conversion*; □ 56% *conversion*; ● 75% *conversion into maltose.*

Further, paper chromatography of the digest showed that sugars other than maltose were not present. It was apparent that, in the hydrolysis of amylose by pure β-amylase at pH 4·6 and 35°, the hydrolysate contains only amylose with a $\overline{\text{D.P.}}$ greater than or equal to that of the original and maltose. Multi-chain action is therefore excluded.

If amylose is attacked only from the non-reducing end then, as has been stressed by Kerr and Gehman,[9] the rate of maltose production should be proportional to the molarity rather than the actual weight concentration of amylose. Accordingly solutions of amylose of varying $\overline{\text{D.P.}}$ but equal molarities should show the same rate of production of maltose. Results of experiments for two $1{\cdot}4 \times 10^{-6}$M-solutions were as shown:

*Conversion (%) into maltose at a given time (min.).*

| $\overline{\text{D.P.}}$ of amylose | 5 | 10 | 15 | 30 | 60 |
|---|---|---|---|---|---|
| 3200 | 34·9 | 44·9 | 55·6 | 71·0 | 77·8 (const.) |
| 2000 | 32·5 | 44·7 | 53·0 | 71·1 | 75·2 (const.) |

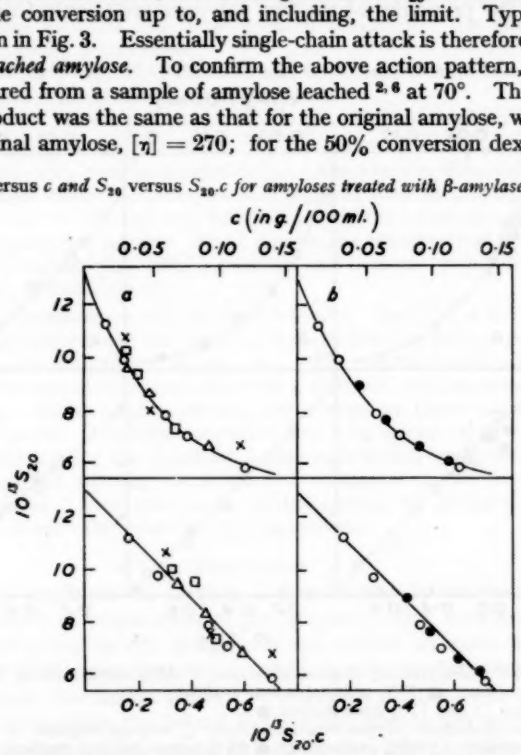
[9] Kerr and Gehman, *Stärke*, 1951, **3**, 271.

These results again substantiate an essentially single-chain action. Similar results have been reported by Kerr and Gehman.[9]

Although it has been reported [10] that oxygen-treatment can introduce barriers to the phosphorolysis of amylose, it was shown elsewhere [1] that amylose prepared in the presence of oxygen was hydrolysed as far as 75% conversion into maltose. The enzymic degradation of this amylose sample was also studied in detail. Fig. 1*c* shows the plots of $S_{20}$ against $c$ and against $S_{20}.c$ for the residual amylose at varying degrees of conversion into maltose. Again, within experimental error, the limiting value of $S_{20}$ for the residual amylose is independent of the conversion up to, and including, the limit. Typical sedimentation diagrams are shown in Fig. 3. Essentially single-chain attack is therefore again established.

(b) *Aqueous-leached amylose.* To confirm the above action pattern, a 50% conversion product was prepared from a sample of amylose leached [2,6] at 70°. The limiting viscosity number of this product was the same as that for the original amylose, within experimental error (for the original amylose, $[\eta] = 270$; for the 50% conversion dextrin, $[\eta] = 265$).

FIG. 2. $S_{20}$ versus $c$ *and* $S_{20}$ versus $S_{20}.c$ *for amyloses treated with β-amylase and Z-enzyme.*




(*a*) *Effect of enzymic hydrolysis*: ○ *original amylose*; × 35% *conversion*; △ 53% *conversion*; □ 64% *conversion into maltose.*
(*b*) *Original amylose* ○ *and* 50% *conversion dextrin* ●.

*Action of β-Amylase and Z-enzyme on Whole Amylose.*—A similar series of investigations was carried out under conditions involving the concurrent action of β-amylase and Z-enzyme and the complete hydrolysis of whole amylose. Fig. 2*a* shows the sedimentation results for the residual amylose at varying degrees of conversion, whilst the corresponding results for a 50% conversion dextrin (isolated from a large-scale experiment) are shown in Fig. 2*b*. Typical sedimentation diagrams are shown in Fig. 3. The properties of the 50% limit and the original amylose were identical, in agreement with Kerr and Cleveland's results,[4] as shown:

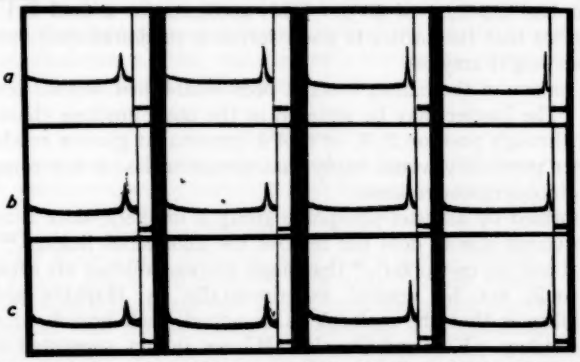
| | $[\eta]$ | Iodine affinity | $10^{13}(S_{20})_0$ |
|---|---|---|---|
| Original amylose ..... | 430 | 19·5 | 13·1 |
| 50% limit dextrin ..... | 425 | 19·6 | 13·1 |

This again substantiates single-chain action.

[10] Baum, Gilbert, and Scott, *Nature*, 1956, **177**, 889.

*Effect of β-Amylase Action on the Absorption Spectra of the Amylose–Iodine Complex.*—Swanson [11] observed that the wavelength of maximum absorption ($\lambda_{max.}$) of the amylose–iodine complex was unaltered during β-amylolysis, thus indicating single-chain action. However, Bourne and Whelan [12] have criticised Swanson's iodine-staining conditions, and found a movement of $\lambda_{max.}$ from 660 to 580 mμ when equal weights of polysaccharide were stained during the formation of 86% of maltose. We have therefore incubated amylose of $\overline{D.P.}$ 3200 with β-amylase, and stained equal weights of residual amylose at intervals up to the production of 84% of maltose. In all samples, the $\lambda_{max.}$ remained unchanged at *ca.* 660 mμ. It now seems probable that Bourne and Whelan's results are due, in part, to contamination of amylose with amylopectin (the β-dextrin of amylopectin [13] has $\lambda_{max.}$ *ca.* 540 mμ), and are not the direct result of multi-chain action. (Amylose prepared recently in this Laboratory by the aluminium hydroxide method [14] contained only 81—87% of amylose.) It should also be noted that iodine-staining measurements on amylose of high $\overline{D.P.}$ (*ca.* 3000) do not enable the reaction mechanism to be determined. (With

FIG. 3. *Tracings of typical sedimentation diagrams. Schlieren wire assembly. In all cases, speed = 60,000 r.p.m.; movement is from right to left; times given are those after reaching full speed; the figures in parentheses after the times indicate the angle of the Schlieren wire.*




(*a*) *Original amylose*: $c = 0{\cdot}14$ g./100 *ml. at* 5 (70°), 9 (65°), 13 (60°), *and* 17 (60°) *min.*
(*b*) 77% *limit dextrin*: $c = 0{\cdot}13$ *g.*/100 *ml. at* 5 (70°), 9 (60°), 13 (60°), *and* 19 (60°) *min.*
(*c*) 50% *conversion dextrin*: $c = 0{\cdot}11$ *g.*/100 *ml. at* 5 (70°), 9 (60°), 14 (60°), *and* 18 (60°) *min.*

single-chain action, no movement of $\lambda_{max.}$ is to be expected, whilst, with multi-chain action, the residual amylose at 84% β-amylolysis would have a $\overline{D.P.}$ of *ca.* 500; $\lambda_{max.}$ for this would be little altered.[3])

*The Action Pattern of β-Amylase.*—All the above results are inconsistent with the concept of multi-chain action. Rather, it appears that, under the conditions of our experiments, the amylose after making contact with a substrate molecule hydrolyses it completely before attacking another molecule, in agreement with Kerr and Cleveland's results.[4] This action is consistent with the remarkably high "turn-over number" (250,000) reported [15] for the enzyme.

Nevertheless, the action pattern appears to differ for short-chain amyloses. Recent studies by Bird and Hopkins [16] have shown that amylose-dextrins ($\overline{D.P.}$ 16—30) were degraded by multi-chain action, whilst Bailey and French [17] found that short-chain

[11] Swanson, *J. Biol. Chem.*, 1948, **172**, 825.
[12] Bourne and Whelan, *Nature*, 1950, **166**, 258.
[13] Fleming and Manners, unpublished results.
[14] Bourne, Donnison, Peat, and Whelan, *J.*, 1949, 1; Hobson, Pirt, Whelan, and Peat, *J.*, 1951, 801.
[15] Englard and Singer, *J. Biol. Chem.*, 1950, **187**, 213.
[16] Bird and Hopkins, *Biochem. J.*, 1954, **56**, 140.
[17] Bailey and French, *J. Biol. Chem.*, 1957, **226**, 1.

XUM

synthetic amyloses were attacked by an intermediary mechanism, whereby several glucosidic linkages are hydrolysed during the enzyme–substrate reaction. It is probable that the relative rate of diffusion of the substrate is a controlling factor in the reaction, since at higher temperatures multi-chain action predominates.[18]

The present study therefore indicates that, at pH 4·6 and 35°, β-amylase degrades amyloses of high molecular weight ($\overline{D.P.} \approx 10^3$) by an essentially single-chain mechanism.

*Order of Reaction.*—Under our experimental conditions, the rate of reaction was so fast that a detailed analysis was not possible. However, the reaction in its initial stages was not of a definite zero or first order (cf. refs. 19 and 20), but the value of $k$ altered. For the overall reaction, the plot [21] of $1/\overline{D.P.}$ against $t$ was not linear. This reaction is being investigated further.

*Nature of the β-Limit Dextrin and the Structure of Amylose.*—As indicated above, amylose in potato starch is heterogeneous both in $\overline{D.P.}$ and in behaviour on β-amylolysis. Our previous results indicate that there is 30—40% of amylose of $\overline{D.P.}$ 1800, which is completely hydrolysed to maltose by *pure* β-amylase. The sample of whole amylose used in this work had a $\overline{D.P.}$ of 3200, and a β-limit of 77%. It therefore follows that the $\overline{D.P.}$ of the presumably incompletely hydrolysed amylose is of the order of 6000, and that, to the first approximation, it has a β-limit of 50%. (This accounts for a final $\overline{D.P.}$ of *ca.* 3000.) A 50% limit suggests that the barrier to β-amylolysis is randomly distributed throughout the high-molecular-weight amylose.

Although the nature of the barrier has not been established, several possibilities have been considered. The barrier may be situated in the main amylose chain itself, or in a side-chain joined through position 2, 3, or 6 of a constituent glucose residue in the main chain. The former possibility would imply that phosphorylase is not completely specific for α-1 : 4-linked glucopyranose residues.

A side-chain formed by an ester-phosphate group is unlikely, since bone phosphatase, which dephosphorylates starch, does not remove the anomalous linkage.[22] Further, the suggestion by Peat and his co-workers [22] that single glucose residues are attached to a main amylose chain could not be verified experimentally by Hopkins and Bird.[23] An alternative possibility is that the molecule is branched, each branch containing several hundred glucose residues. Kerr and Cleveland [24] have, in fact, suggested that potato and tapioca amylose are singly branched, and contain 1—3 branches per molecule. Our previous studies [1] suggest that, if branching occurs, the interchain linkage is not of the α-1 : 3- or α-1 : 6-type.

It must be noted that amyloses from a wide variety of plant starches contain anomalies which are resistant to β-amylase.[25] Individual amyloses appear to differ in both $\overline{D.P.}$ and β-amylolysis limit, indicating that variations exist in the relative proportion and distribution of the barriers to β-amylolysis.

The authors thank Professor E. L. Hirst, F.R.S., for his interest in this work and the Rockefeller Foundation for financial support. Thanks are also offered to the D.S.I.R. for a maintenance grant (to I. D. F.).

CHEMISTRY DEPARTMENT,
THE UNIVERSITY, EDINBURGH, 9. [*Received, July 18th*, 1957.]

[18] Whelan, *Biochem. Soc. Sympos.*, 1953, **11**, 17.
[19] Hopkins and Jelinek, *Biochem. J.*, 1948, **43**, 32.
[20] Kerr and Severson, *J. Amer. Chem. Soc.*, 1943, **65**, 193.
[21] Bryce and Greenwood, *J. Polymer. Sci.*, 1957, **25**, 480.
[22] Peat, Thomas, and Whelan, *J.*, 1952, 722.
[23] Hopkins and Bird, *Nature*, 1953, **172**, 492.
[24] Kerr and Cleveland, *J. Amer. Chem. Soc.*, 1952, **74**, 4036.
[25] Manners, *Quart. Rev.*, 1955, **9**, 82; Neufeld and Hassid, *Arch. Biochem. Biophys.*, 1955, **59**, 405; Arbuckle and Greenwood, unpublished experiments.

## 136. *Physicochemical Studies on Starches. Part X.* The Molecular Weight of the Water-soluble Polysaccharides of Sweet Corn,* Zea mays.

By C. T. Greenwood and P. C. Das Gupta.

Detailed results are given of physical studies on samples of the water-soluble glucosans of sweet corn, *Zea mays*, isolated by Peat, Whelan, and Turvey.[1] Another sample of the total water-soluble polysaccharide has also been prepared. The glucosan-product had a very high molecular weight, and, further, on dissolution and fractionation with 67% acetic acid gave only 2% of the total as " soluble " material. It is therefore suggested that in the sample of seed examined the water-soluble glucosan is essentially *homogeneous*, and has a molecular weight of the order of $30 \times 10^6$, and an average length of unit chain of 14. The structure of the glucosan is discussed in relation to that of glycosan and amylopectin.

Recently, Peat, Whelan, and Turvey [1] carried out a comprehensive study of the water-soluble amylaceous polysaccharides of sweet corn (*Zea mays*), in which they established the conditions necessary to avoid extensive enzymic degradation of polysaccharide during isolation. A full review of the previous literature was also given. In this paper, we report details of the physical measurements carried out on the samples kindly placed at our disposal by Professor S. Peat, together with the results of our own investigations on the isolation and fractionation of *Zea mays* glucosans.

### Experimental

All samples were dried at 80° *in vacuo* before analysis. The carbohydrate content of the polysaccharide was determined by acid hydrolysis (0·5N-sulphuric acid for 7 hr. at 98°), followed by the estimation of the amount of liberated glucose by alkaline ferricyanide.[2] Nitrogen estimations were by the semimicro Kjeldahl method.

*Isolation of the Water-soluble Polysaccharides of* Zea mays.—Mature *Zea mays* (*var.* Golden Bantam; 400 g.) was ground and extracted with 0·01N-mercuric chloride as described by Peat *et al.*[1] Extracts were filtered through muslin, and the starch allowed to settle before the supernatant liquors were passed through the Sharples supercentrifuge and concentrated to $\frac{1}{10}$ vol. (under reduced pressure at 30°). Coagulated protein and any other insoluble material were then removed by careful filtration, and the soluble polysaccharide precipitated by the addition of ethanol (1·5 vol.) at 0°. The precipitate was removed on the centrifuge, washed with acetone and ether and dried (yield 79 g.) (Found: N, 0·32; carbohydrate, 88·8%.) The sugar-containing supernatant liquid was treated as by Peat *et al.*,[1] to yield approximately 13 g. of material, which contained no polysaccharide disclosed by chromatography.

*Fractionation of the Water-soluble Polysaccharide.*—Water-soluble polysaccharide (22 g.) was dissolved in water (300 ml.) and cooled to 0°, and glacial acetic acid (600 ml.) was added slowly with stirring, the temperature being kept *at* 0° *during the whole period*. After the mixture had been then kept at −2° for 18 hr., the precipitated phytoglycogen-A was removed on a refrigerated centrifuge (at 0°), and washed well with acetone to remove the acid. (Isolation of the material by centrifugation at room temperature caused slightly more degradation, as shown by a decrease in sedimentation constant from 226*s* to 214*s*.) After dissolution in water, the pH was adjusted to 6·5 with sodium hydroxide before reprecipitation of the polysaccharide by the addition of ethanol (1·5 vol.). The product was washed with ethanol and with ether and dried (yield 20·5 g.) (Found: N, 0·2; carbohydrate, 92%). The phytoglycogen-B was isolated from the original supernatant liquor by the addition (at 0°) of ethanol (0·5 vol.) (yield 0·83 g.) (Found: N, 1·0; carbohydrate, 47%).

*Attempted Removal of Protein and Fractionation of the Water-soluble Polysaccharide.*—Polysaccharide was dissolved in 0·1M-sodium chloride (8% solution) and shaken overnight with toluene ($\frac{1}{10}$ vol.). The toluene layer was then allowed to separate and was removed. The

* Part IX, preceding paper.

[1] Peat, Whelan, and Turvey, *J.*, 1956, 2317.
[2] Lampitt, Fuller, and Coton, *J. Sci. Food Agric.*, 1955, **6**, 656.

XUM

process was repeated until the amount of coagulated material in the toluene layer was negligible. The solution was then cooled to 0°, divided into 3 portions, and treated as follows: (i) the polysaccharide was precipitated with ethanol (1·5 vol.), washed with ethanol and with ether, and dried (Found: N, 0·09%); (ii) phytin was removed by acidifying the solution with hydrochloric acid (1%) and precipitating the polysaccharide immediately; [1] the polysaccharide was then isolated after adjustment of the pH of the solution to 6·5 as above; (iii) phytoglycogen-A and -B was obtained by the addition of glacial acetic acid (2 vol.) as above; phytoglycogen-A was purified from phytin and adhering acid; again the yield of phytoglycogen-B was small, and it was difficult to isolate this material by precipitation.

*Characterization of the Polysaccharide Fractions.*—Measurements of (i) average length of unit chain by periodate oxidation, (ii) iodine affinity, and (iii) sedimentation velocity in 0·2M-sodium chloride were carried out as described in previous papers in this Series. The sedimentation constant ($S_{20}$) for the polysaccharides was found to be the same in water and in 0·2M-aqueous sodium chloride, and measurements have been made in both solvents. $S_{20}$ was a linear function of $c$; its dependence on concentration is expressed here by values of $k$ in the equation $S_{20} = (S_{20})_0(1 - kc)$, where $(S_{20})_0$ is the sedimentation constant at infinite dilution.

*Determination of Diffusion Coefficient* (with W. A. J. Bryce).—The diffusion coefficient of the polysaccharides dissolved in 0·2M-sodium chloride was measured in a new type of diffusion cell designed for the Antweiler microelectrophoresis and diffusion apparatus. In this instrument, the refractive-index gradient curve is measured by means of a Jamin interferometer. Diffusion coefficients ($D_m$) were calculated by the moment method. Measurements were carried out at 20°. Details of the apparatus and method will be presented elsewhere.

*Light-scattering Measurements* (with I. G. Jones).—Measurements were made with a Brice–Phoenix Photometer (Model 1000D), with cylindrical cells and the narrow diaphragm system.[3] Turbidities ($\tau$) were determined by the "working standard" method. The dissymmetry ratio ($I_{45°}/I_{135°}$; corrected for back-reflection) was also measured. Solvent (0·1M-sodium chloride) was filtered through sintered glass (G5) directly into the scattering cell. Polysaccharide solutions (approx. 0·1%) were filtered through sintered glass (G4), and successive aliquot parts of the clarified solution were added to a weighed amount of solvent in the scattering cell to form a concentration series in the range (1—20) × $10^{-5}$ g./ml. [Concentrations ($c$ in g./ml.) were estimated by hydrolysing a portion of the original filtered solution, and estimating the amount of liberated glucose by the alkaline ferricyanide–ceric sulphate method.[2]] This

Table 1. *The properties of Peat, Whelan, and Turvey's polysaccharides.*[1]

| Polysaccharide | Extraction [a] | Carbohydrate (%) [b] | Unit chain length | Slope of iodine titration [c] | $k$ [d] | $10^{13}(S_{20})_0$ [e] | $10^7 D_m$ | $10^{-6}M$ |
|---|---|---|---|---|---|---|---|---|
| Phytoglycogen A ..... | + | 94·2 | 13·2 | 0·017 | — | (185) | — | (20) |
| ,, ,, ..... | — | 95·1 | 9·7 | 0·007 | — | (55) | — | (6) |
| ,, B ..... | + | 94·7 | 7·3 | 0·007 | — | (48) | — | (4) |
| ,, ,, ..... | — | 93·8 | 5·8 | 0·000 | — | (2·3) | — | — |
| *Fractions* | | | | | | | | |
| 55—60% AcOH ppt. | + | — | 10·3 | — | 0·07 | 146 | 0·6 | 15 |
| 60—65% ,, | + | — | 11·0 | — | 0·09 | 131 | — | (14) |
| 65—70% ,, | + | — | 9·7 | — | 0·15 | 78 | — | (8) |
| >70% ,, | + | — | 7·8 | — | 0·75 | 9 | 3·5 | 0·2 |

[a] Extraction with (+) or without (−) $HgCl_2$. [b] Values from ref. 1. [c] Slope of linear portion of iodine titration curve. Values from Part III.[4] [d] Value of $k$ in the equation $S_{20} = (S_{20})_0(1 - kc)$, where $c$ = g./100 ml. [e] Values in parentheses were determined at a concentration of 0·5 g. per 100 ml. Calc. from $M = RT(S_{20})_0/(1 - \overline{V}\rho)D_m$, where $\overline{V}$ = partial specific volume = 0·62, the value found for glycogen (unpublished results). For the values in parentheses, $D_m$ has been assumed to be 0·6 × $10^{-7}$.

procedure gave solutions which showed reproducible turbidities, and, on the whole, reproducible low dissymmetries. (Large dissymmetries occasionally observed were thought to be due to anomalous aggregates which were not removed by filtration.) Molecular weights ($M$) were calculated from the equation:

$$Hc/\tau = 1/M(P_{90°}) + 2B(P_{90°})c/RT \text{ where } H = 32\pi^2n^2(dn/dc)^2/3\lambda^4N;$$

[3] Brice, Halwer, and Speiser, *J. Opt. Soc. Amer.*, 1950, **40**, 768.

($P_{90°}$) is the particle scattering factor, and was calculated from the dissymmetry on the assumption that the molecules are spherical; [4] $B$ is a constant. The refractive index increment ($dn/dc$) was measured at 546 mμ on a Brice–Phoenix differential refractometer,[5] and a value of 0·146 was found. Within experimental error, ($Hc/\tau$) was independent of $c$ for the range of concentrations studied, and hence the term $2B(P_{90°})c/RT$ was negligible. The reproducibility of results for a given sample is indicated in Table 3.

TABLE 2. *The properties of the polysaccharides isolated in this work.*

| | Total polysaccharide * | | Phytoglycogen A * | | Phytoglycogen B * |
|---|---|---|---|---|---|
| | (*a*) | (*b*) | (*a*) | (*b*) | (*b*) |
| Carbohydrate (%) ..... | 92 | 100 | 92 | 97 | 83 |
| Length of unit chain ..... | 14·0 | 14·0 | 13·0 | 13·0 | 11·3 |
| $k$ † ..... | 0·025 | 0·025 | 0·025 | — | 0·75 |
| $10^{13}(S_{20})_0$ ..... | 252 | 242 | 226 | — | 8 |
| $10^7 D_m$ ..... | — | 0·53 | — | — | — |
| $10^{-6}M$ ..... | (30) ‡ | 29 | (27) ‡ | — | (0·14) ‡ |

* (*a*) Purified free from protein; (*b*) purified free from protein and phytin. † As in Table 1.
‡ Calc. by assuming $D_m = 0·53 \times 10^{-7}$ for total polysaccharide and phytoglycogen A, and $D_m = 3·5 \times 10^{-7}$ for phytoglycogen B.

TABLE 3. *Results of light-scattering measurements.*

| Sample | Ref. | Uncorrected $M(\times 10^{-6})$ | Dissymmetry | $1/(P_{90°})$ | Corrected $M(\times 10^{-6})$ |
|---|---|---|---|---|---|
| Phytoglycogen A ..... | 1 | 18 | 3·0 | 2·0 | (21) * |
| „ B ..... | 1 | 4 | 1·18 | 1·12 | 4·5 |
| | | 3·9 | 1·16 | 1·11 | 4·3 |
| 55—60% AcOH fraction ... | 1 | 18 | 3·0 | 2·0 | (21) * |
| Total polysaccharide ..... | This work | 22 | 1·26 | 1·17 | 26 |
| | | 22 | 1·45 | 1·28 | 28 |

* Calc. by assuming a particle-scattering factor of 1·17.

*Results.*—The properties of the polysaccharide samples supplied by Professor Peat [1] are shown in Table 1. Table 2 shows the corresponding properties of our own samples. Table 3 summarizes the light-scattering data.

The results of typical sedimentation experiments are shown in the Figure.

## DISCUSSION

Our lower yield of water-soluble polysaccharide (cf. ref. 1) is not thought to be due to degradation, since the amount of simple sugars was low, and the molecular weight of the product was high; it is more probable that the amount of this polysaccharide present in the seed varies.

Previous workers (see ref. 1) have suggested that 67% acetic acid separates the water-soluble polysaccharide into two fractions of different properties. Peat, Whelan, and Turvey [1] have shown that these fractions are similar and that, by minimizing enzymic degradation, the percentage of insoluble fraction (phytoglycogen A) is increased. They concluded that the acetic acid was causing a simple molecular-weight fractionation. However, from the batch of seed used we have isolated a glucosan with a larger molecular weight than the phytoglycogen A of these workers, and our yield of soluble polysaccharide (phytoglycogen B) was less than 2% of the total. On this basis, we suggest that this sample of water-soluble polysaccharide might well be essentially *homogeneous* [see the sedimentation diagrams (*g*) in the Figure].

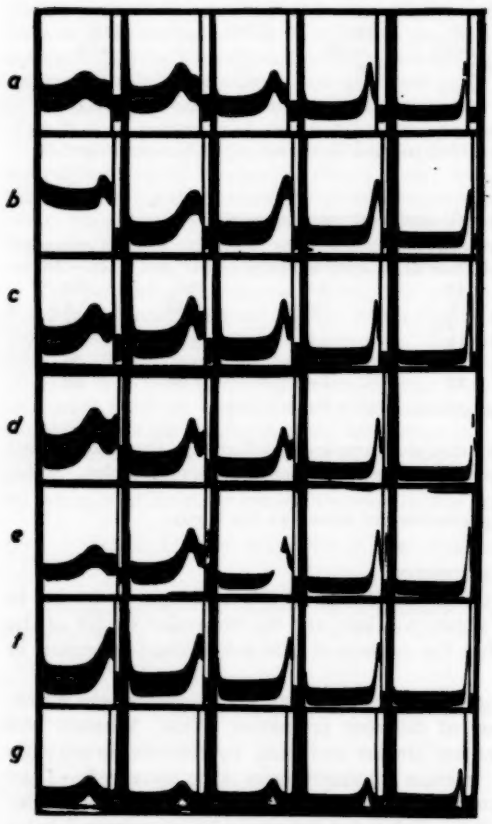
*Molecular Weights of the Water-soluble Polysaccharide and its Fractions.*—For most of the samples, the agreement between molecular weight as measured by sedimentation and diffusion and by light-scattering is good. This suggests that true molecular weights are being measured. The general conclusions drawn by Peat and his co-workers [1] regarding

[4] Doty and Steiner, *J. Chem. Phys.*, 1950, **18**, 1211.
[5] Brice and Halwer, *J. Opt. Soc. Amer.*, 1951, **41**, 1033.
[6] Part III, *J.*, 1955, 3016.

XUM

the drastic effect of enzymic degradation during isolation—unless precautions are taken to avoid this—are completely substantiated from a comparison of the molecular weights quoted in Table 1. These values are larger than the previous relative ones since the diffusion constant was smaller than estimated. Nearly all the samples are somewhat polydisperse on ultracentrifugation [see diagrams (*a*)—(*f*) in the Figure]. This suggests that material of low molecular weight may be present, or that some degradation had

*Typical sedimentation diagrams. All samples from Peat, Whelan, and Turvey*[1] *[except (g)]. The concentration is* 1·0 g./100 ml. *except for (g) where it is* 0·5 g./100 ml. *Sedimentation is from right to left. The figures in parentheses after the times indicate the angle of the Schlieren bar.*




*Phytoglycogen A*: *speed* = 20,000 *r.p.m.*; 2(65°), 4·5(50°), 9·5(40°), 13·5(30°), *and* 18·5(30°) *min. after reaching full speed.*

*Phytoglycogen B*: *speed* = 20,000 *r.p.m.*; 2·5(70°), 6(60°), 10(45°), 16·5(30°), *and* 24(30°) *min. after reaching full speed.*

55—60% AcOH *fraction*: *speed* = 20,000 *r.p.m.*; 1(65°), 4(50°), 7(35°), 12(25°), *and* 17(25°) *min. after reaching full speed.*

60—65% AcOH *fraction*: *speed* = 20,000 *r.p.m.*; 2(65°), 5(50°), 10(40°), 14(30°), *and* 22(20°) *min. after reaching full speed.*

65—70% AcOH *fraction*: *speed* = 20,000 *r.p.m.*; 5(60°), 8·5(50°), 20(35°), 25(30°), *and* 36(30°) *min. after reaching full speed.*

>70% AcOH *fraction*: *speed* = 20,000 *r.p.m.*; 10(60°), 20(45°), 32(35°), 48(30°), *and* 65(25°) *min. after reaching full speed.*

*Whole water-soluble polysaccharide*: *speed* = 15,000 *r.p.m.* 5(70°), 9(60°), 12(55°), 15(55°), *and* 17(45°) *min. after reaching full speed.*

occurred during both isolation and subfractionation. The values for the subfractions (Table 1) may suggest that a good separation of products of different molecular weight was not obtained.

The molecular weight of the total water-soluble polysaccharide from the sample of seed examined is about $30 \times 10^6$ (*i.e.*, $\overline{\text{D.P.}} \approx 180{,}000$). This value is larger than that reported for glycogens,[7] with the exception of the recent work by Stetten, Katzen, and Stetten.[8] The frictional ratio ($f/f_0 = 2$; calculated from the sedimentation and diffusion results) indicated that in solution the polysaccharide was heavily hydrated or was not spherical.

[7] For review see Greenwood, *Adv. Carbohydrate Chem.*, 1952, **7**, 289; 1956, **11**, 385.
[8] Stetten, Katzen, and Stetten, *J. Biol. Chem.*, 1956, **22**, 587.

*Structure of the Water-soluble Polysaccharide.*—Our periodate oxidation results (chain-length = 14) are in general agreement with those of Peat and his co-workers.[1] These authors suggested that the polysaccharide must possess a glycogen-type structure. It is certainly true that the sedimentation behaviour is similar to that of glycogen rather than of amylopectin. (We have shown recently [9] that, whereas $S_{20}$ is virtually independent of $c$ for glycogens, for amylopectin $S_{20}$ is very strongly dependent for $c$. This must be related to differences in shape of the two molecules.) However, a considerable difference occurs between the iodine-binding power of this type of polysaccharide and of glycogen. We suggested previously [6] that, since the uptake was 3—4 times greater than for a glycogen of corresponding chain-length, the structure of the two polysaccharides differs in that the degree of multiple-branching of the water-soluble material is intermediate between those for glycogen and for amylopectin. However, in view of unit-chain-length, enzymic degradation experiments,[1] and sedimentation behaviour, the polysaccharide appears to be nearer in structure to a glycogen than an amylopectin.

The authors thank Professor E. L. Hirst, F.R.S., for his interest and advice, Professor S. Peat, F.R.S., for valuable comments on the manuscript, and the Commonwealth Relations Office, Government of U.K., and the Indian Central Jute Committee for a Scholarship (to P. C. D. G.).

CHEMISTRY DEPARTMENT,
THE UNIVERSITY, EDINBURGH, 9. [*Received, July 18th*, 1957.]

[9] Bryce, Cowie, and Greenwood, *J. Polymer Sci.*, 1957, **25**, 251.

---

## 137. *Physicochemical Studies on Starches. Part XI.* The Granular Starch of Sweet Corn,* Zea mays.

By C. T. GREENWOOD and P. C. DAS GUPTA.

The starch present in sweet corn, *Z. mays*, has been isolated in granular form and obtained free from protein. It has been fractionated into its component amylose and amylopectin, and some physical properties of these fractions, including estimations of molecular weight, are described.

IN view of recent interest [1] in the structure of the water-soluble glucosans of sweet corn (*Zea mays*), we have examined the *granular* starch which co-exists in the cereal grain. No detailed study of this starch appears to have been made previously.

### EXPERIMENTAL

*Isolation of Starch.*—Mature *Zea mays* (var. Golden Bantam; 300 g.) was ground to a coarse powder (Found: $H_2O$, 12·3; ash, 1·81; N, 1·86%) and exhaustively extracted with boiling benzene–methanol (2 : 1 v/v; 2 l.) (Found: loss in wt., 12·3%). Defatted grain was then shaken vigorously with 0·1M-sodium chloride (1·5 l.; 5 × 6 hr.) under toluene, the aqueous suspensions filtered through muslin, and crude starch (A) allowed to settle (Found: N, 1·38%).

*Removal of Protein from Starch A.*—The crude starch was suspended in 1M-sodium chloride, then treated with toluene as previously described.[2] The process was repeated to yield starch B, which was stored in saline under toluene at 0° (yield, 5% of original dry wt. of grain) (Found: N, 0·13%).

*Properties of Starch B.*—On hydrolysis with 2% sulphuric acid, the starch yielded 96% of the theoretical amount of glucose (quantitative chromatography), and no other sugar was detected on the paper chromatogram. This material had $[\alpha]_D^{17}$ +152° ($c$ 0·77% in N-NaOH).

* Part X, preceding paper.

[1] Peat, Whelan, and Turvey, *J.*, 1956, 2317, and references therein.
[2] Greenwood and Robertson, *J.*, 1954, 3769.

XUM

The optical density of the colour developed when starch (1 mg.) was stained with iodine (2 mg.) and potassium iodide (20 mg.) in distilled water (100 ml.) and measured at 6800 Å in cells of 2 cm. length (against the same iodine solution by means of a Unicam spectrophotometer) was 0·23. The iodine affinity of the starch (see below) was 5·5%, corresponding to 28% of amylose, whilst the average length of unit chain of the amylopectin was shown by calculation from the results of periodate oxidation [3] of the whole starch, and of the isolated amylopectin, to be 23 glucose residues.

Starch B was used in all further investigations.

*Fractionation Methods.*—Attempts were made to fractionate the *Z. mays* starch by the methods previously described in this Series: (i) dispersion in water at 98° followed by the addition of thymol as precipitant and butan-1-ol as the recrystallisation agent,[4] (ii) aqueous leaching at 70° followed by dispersion of the residue at 98° and addition of butan-1-ol,[4] and (iii) pretreatment of the granules with M-potassium hydroxide at 0°, before neutralization and dispersion and the addition of pentyl alcohol.[5,6]

*Characterisation of the Components.*—These were characterized by (i) potentiometric titrations to determine iodine affinity,[7] (ii) measurements of limiting viscosity number $[\eta]$ in M-potassium hydroxide,[8] and (iii) measurements of sedimentation velocity in 0·2M-potassium hydroxide.

*Measurement of Sedimentation Velocity.*—Rates of sedimentation of the two components in 0·2M-potassium hydroxide were determined by using a " Spinco " electrically driven ultracentrifuge (Spinco Division, Beckman Instruments Corporation, Belmont, California). Measurements were made in a 12 mm. cell incorporating a Kel-F centrepiece. The initial experiments with alkali as a solvent for the components [9] showed that the optimum speed for solutions of amylose of concentration greater than 0·1 g./100 ml. was 60,000 r.p.m., whilst for more dilute solutions, 30,000 r.p.m. was more suitable. Amylopectin solutions were spun at either 15,000 r.p.m. or 12,600 r.p.m. depending on the concentration. The pressure in the vacuum-chamber was less than 1 μ Hg, and the temperature rise in the rotor was about 0·6°/hr. at 60,000 r.p.m. and correspondingly less for lower speeds. (The refrigerating system was not utilized.) Runs were normally complete within 30 min. The temperature of the rotor was measured before and after the completion of each run, and the temperature at any time during the run obtained by linear interpolation. A correction was applied to allow for the adiabatic cooling of the rotor during acceleration.[10,11] A modified Philpot–Svensson optical system enabled movement of the boundaries to be followed directly. The magnification of this lens system was shown to be constant over the whole field. The distance from the reference line of the optical system to the axis of rotation was 5·730 cm. Measurements of the rates of sedimentation were made by measuring the position of the boundary to 0·01 mm. directly from the photographic plates, a two-dimensional travelling microscope being used. Sedimentation constants ($S$) were evaluated from the equation: $\mathrm{d}(\log_{10} X/\omega^2)\mathrm{d}t = S/2{\cdot}303$, $X$ being in cm. from the centre of rotation, $t$ the time from the start of the acceleration in sec., and $\omega$ the angular velocity in radians. In this manner, linear graphs of $\mathrm{d}\log_{10} X$ against $t$ were obtained: the point where the lines cut the time-axis at the value of $\mathrm{d}\log_{10} X$ for the meniscus, representing the time required before sedimentation started (*i.e.*, approx. two-thirds of the acceleration period). Results were corrected [12] to water at 20°.

*Diffusion Measurements.*—The method is outlined in Part X.[13] The solvent was 0·2M-potassium hydroxide, and values of the diffusion constant ($D_m$) were calculated by the moment method.

## Results and Discussion

*Zea mays* starch has been isolated in granular form, reagents likely to cause degradation being avoided. Contamination with protein was reduced to 0·8% under the necessary

[3] Anderson, Greenwood, and Hirst, *J.*, 1955, 225.
[4] Cowie and Greenwood, *J.*, 1957, 2862.
[5] Cowie and Greenwood, *J.*, 1957, 4640.
[6] Potter, Silveira, McCready, and Owens, *J. Amer. Chem. Soc.*, 1953, **75**, 1335.
[7] Anderson and Greenwood, *J.*, 1956, 3016.
[8] Cowie and Greenwood, *J.*, 1957, 2658.
[9] Brice, Cowie, and Greenwood, *J. Polymer Sci.*, 1957, **25**, 251.
[10] Waugh and Yphantis, *Rev. Sci. Instr.*, 1952, **23**, 609.
[11] Biancheria and Kegeles, *J. Amer. Chem. Soc.*, 1954, **76**, 3737.
[12] Svedberg and Pedersen, " The Ultracentrifuge," Oxford Univ. Press, 1940.
[13] Greenwood and Das Gupta, preceding paper.

mild conditions by the technique previously described.[2] However, purely physical methods did not further reduce the protein content. This phenomenon has been encountered [14] during the isolation of a large number of starches. The significance of the protein is doubtful, although it may well be incorporated into the granular structure.

The starch proved difficult to disperse in hot water. This is a feature which has been found in this laboratory to be common to a large number of cereal starches. Its significance with regard to granular structure is not yet known. The apparent resistance of the granule made its fractionation difficult. Conventional aqueous dispersive and leaching methods of fractionation were, in fact, unsuccessful, and the method involving preliminary swelling in M-potassium hydroxide [5,6] had to be used. The properties of the components from the most effective separation achieved by this method were as shown in the Table.

*Properties of* Z. mays *starch components.*

| | Iodine affinity [a] | Purity (%) | $[\eta]$ in M-KOH | $10^{13}(S_{20})_0$ [b] | $\overline{M}_{s,D}$ [c] | $\overline{M}_n$ |
|---|---|---|---|---|---|---|
| Amylose | 18·8 [d] | 100 | 150 | 5·2 | 317,000 | 180,000 |
| Amylopectin | 0·3 | 98 | 100 | 275 | — | — |

[a] See ref. 7. [b] Values obtained by graphical extrapolation, see text. [c] Calc. from $\overline{M}_{s,D} = RT(S_{20})_0/(1 - \overline{V}\rho)D_m$.
[d] Constant on further recrystallization.

The iodine affinity of the amylose is slightly lower than that for potato amylose, but similar to that found for other cereal starches in this laboratory. Barriers to β-amylolysis are present. Enzymic experiments carried out by Mr. A. W. Arbuckle showed that treatment with pure β-amylase resulted in only 78% conversion into maltose, a value very similar to the 77% limit reported for potato amylose.[15] The concurrent action of β-amylase and Z-enzyme resulted in 100% conversion, thus giving a further check that the amount of amylopectin impurity was negligible.

As reported previously,[9] the sedimentation constant ($S_{20}$) for both components is strongly dependent on the concentration $c$ (see Figure). For amylose, the extrapolation to infinite dilution was simplified by plotting $S_{20}$ against $S_{20}.c$ as well as against $c$. The resultant value $(S_{20})_0$ was $5{\cdot}2 \times 10^{-13}$ c.g.s. units. The diffusion coefficient ($D_m$) at $c = 0{\cdot}2$ g./100 ml. was measured by Mr. W. A. J. Bryce who found $D_m = 1{\cdot}0 \times 10^{-7}$, and hence, when the partial specific volume ($\overline{V}$) of amylose in this solvent [16] is taken to be 0·60, the molecular weight of the amylose ($\overline{M}_{s,D}$) is 317,000 and its D.P. = 1950. Calculation of the number-average molecular weight ($\overline{M}_n$) from the viscosity data by the relation previously obtained for potato amylose [4] gave $\overline{M}_n$ 180,000 and D.P. 1100. These values are lower than those for potato amylose.

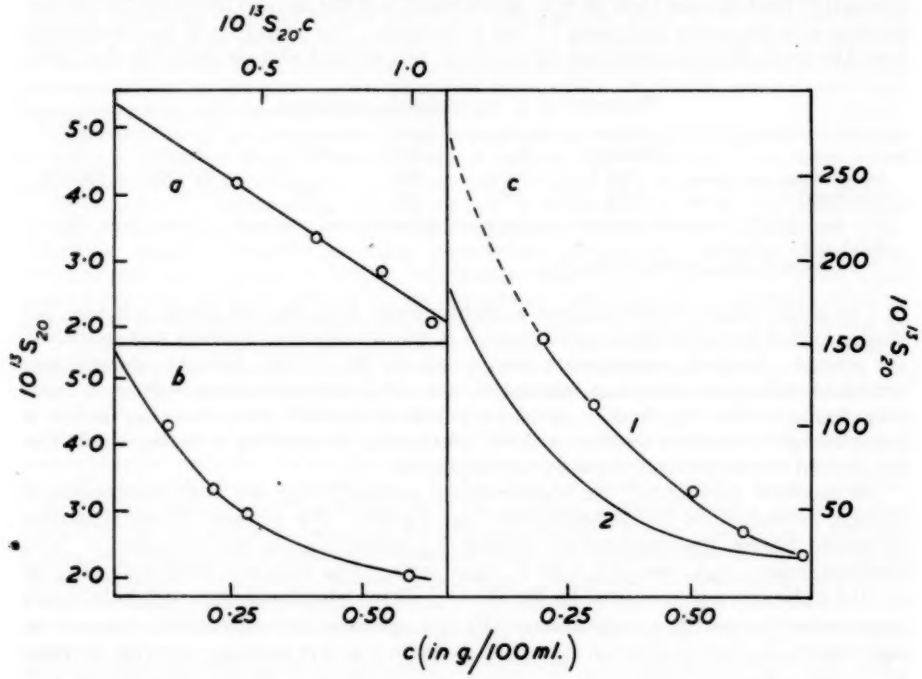
Whilst the sedimentation diagrams for the amylose were well defined at low dilutions, those for the amylopectin showed a great tendency to spread and so make measurement of the mean position of the peak difficult. In view of the extreme concentration dependence, no attempt was made to extrapolate $S_{20}$ accurately to infinite dilution, but for comparison our previous results [9] for potato amylopectin are also shown in the Figure. Although without knowledge of the diffusion coefficient the molecular weight cannot be estimated, this would appear to be greater than for potato amylopectin for which values of $36 \times 10^6$ have been found.[17] This extreme size might well cause the difficulties in dispersion and fractionation of the starch. Ultracentrifugal examination of some of the more impure amylopectins showed two peaks, in agreement with Stacy and Foster's recent results.[18] However, any appreciable amylose impurity (greater than about 5%) is

[14] Anderson and Greenwood, unpublished results.
[15] Cowie, Fleming, Greenwood, and Manners, *J.*, 1958, 697.
[16] Bryce and Greenwood, unpublished results.
[17] Witnauer, Senti, and Stein, *J. Polymer. Sci.*, 1955, **16**, 1.
[18] Stacy and Foster, *ibid.*, 1957, **25**, 39.

XUM

sufficient to distort completely the sedimentation diagram at low concentrations of amylopectin. This phenomenon, together with boundary anomaly effects,[19] makes reliable estimates of $S_{20}$ and its consequent extrapolation to infinite dilution impossible. Experience in this laboratory has shown that ultracentrifugal analysis of impure amylopectins is most unsatisfactory (cf. ref. 18).

*The variation of sedimentation constant ($S_{20}$) with concentration ($c$) for (a) amylose, $S_{20}$ versus $S_{20}.c$, (b) amylose, $S_{20}$ versus $c$, (c) amylopectin, $S_{20}$ versus $c$ for (1) Z. mays and (2) potato.*




The granular starch in *Z. mays* is obviously a typical cereal starch, and its properties are completely unaltered by the co-existence in the cereal grain of the glycogen-like water-soluble glucosans.[1,13]

The authors thank Professor E. L. Hirst, F.R.S., for his interest, and the Commonwealth Relations Office, Government of U.K., and the Indian Central Jute Committee for a Scholarship (to P. C. D. G.).

Department of Chemistry,
The University, Edinburgh, 9. [*Received, August 12th*, 1957.]

[19] See, *e.g.*, Trautman, Schumaker, Harrington, and Schachman, *J. Chem. Phys.*, 1954, **22**, 555.

# 138. *Physicochemical Studies on Starches. Part XII.* The Molecular Weight of Glycogens in Aqueous Solution.*

By W. A. J. Bryce, C. T. Greenwood, I. G. Jones, and D. J. Manners.

Molecular weights are presented for 23 samples of glycogens isolated from various biological sources. Ultracentrifugal analysis showed that most of the samples were polydisperse. The molecular weights of the main components lie in the range (3—9) × $10^6$. The polydisperse nature of the glycogens has been confirmed by light-scattering measurements. The effects of varying the isolation procedure, and of alkali, on the molecular weight have also been studied.

Glycogen and amylopectin are both highly branched, essentially α-1 : 4-linked glucosans. However, their hydrodynamic properties are completely different. This must be related to fundamental differences in fine structure and molecular shape.[1,2] In this paper, we describe the solution properties and hydrodynamic behaviour of glycogens isolated from a variety of biological sources. Estimations of molecular weight and its distribution have been obtained, and the effects of variations in the method of isolation, and of alkali, on the molecular weight have been studied. A preliminary account of some of this work has already appeared.[3]

## Experimental

*Sedimentation Measurements.*—The methods described in Part XI [4] were employed. M- and 0·1M-sodium chloride and 0·2M-potassium hydroxide were used as solvents.

The sedimentation constant ($S_{20}$) was virtually independent of the solvent, and the majority of the measurements were carried out in either M- or 0·1M-sodium chloride. Results were corrected to water at 20°.

The apparent amount of each component in a resolvable polydisperse system was estimated by direct measurement of the areas under the refractive-index gradient curves. An enlarged image (3×) of the photographic plates was projected on smooth paper and the upper outline traced. An image of the base line (from a comparative run with solvent alone in the cell) was then superimposed by alignment of the reference lines, and traced on. The refractive-index gradient curves were carefully divided, in the usual manner, on the assumption that each component had a symmetrical distribution, and the appropriate areas between the peaks and the base-line were measured with a planimeter. Values were expressed to the nearest 5%.

Estimations of the polymolecularity of the major component of some of the glycogen samples were obtained by using Gralen's function,[5] $dB/dX$, where $B$ is an estimate of the "width" of the sedimentation gradient curve and is equal to $H/A$ ($A$ = area of the Schlieren diagram; $H$ = the height of the maximum ordinate), and $X$ = the distance of the peak from the axis of rotation. In all instances, $B$ varied linearly with $X$. Although this function should be extrapolated to infinite dilution, the value at $c$ = 1 g. per 100 ml. was taken as a standard for comparison of the polymolecularity of different samples.

*Diffusion Measurements.*—The method is outlined in Part X.[6] The solvent was 0·1M-sodium chloride, and values of the diffusion constant ($D_m$) were calculated by the moment method.

*Partial Specific Volume.*—The partial specific volume ($\bar{V}$) of glycogen was taken as 0·62, the value calculated from density measurements on aqueous solutions of one sample.

*Light-scattering Measurements.*—The apparatus and the methods used to clarify and dilute the glycogen solutions were similar to those previously described for the *Zea mays* polysaccharides,[6] 0·1M-sodium chloride being the solvent. Although 15% aqueous magnesium

* Part XI, preceding paper.

[1] Part IV, Bryce, Cowie, and Greenwood, *J. Polymer Sci.*, 1957, **25**, 251.
[2] Greenwood, *Adv. Carbohydrate Chem.*, 1956, **11**, 335; Manners, *ibid.*, 1957, **12**, 261.
[3] Greenwood and Manners, *Proc. Chem. Soc.*, 1957, 26.
[4] Preceding paper.
[5] Gralén, Inaugural Diss., Uppsala, 1944.
[6] Part X, Greenwood and Das Gupta, *J.*, 1958, 703.

XUM

chloride has been recommended,[7,8] we found this solvent to have no advantages. The value of the molecular weight of a given sample was the same in both the above solvents. Glycogen solutions were clarified by careful filtration (cf. ref. 8) through sintered glass (G4). Repeated filtration caused some small loss in turbidity, whilst little improvement occurred in the apparent dissymmetry. (For example, a sample after one filtration had $M = 8{\cdot}4 \times 10^6$, dissymmetry = 1·41; after five filtrations, $M = 7{\cdot}7 \times 10^6$, dissymmetry = 1·34, the concentration being assumed to be unchanged by filtration.) Solutions were therefore filtered once, before dilution. This procedure gave reproducible results. $Hc/\tau$ was independent of $c$ for all samples. The particle scattering factor ($P_{90°}$) was calculated from the dissymmetry, the molecules being assumed to be spherical.[6] The refractive-index increment ($dn/dc$) for glycogen was found to be 0·146 ($c$ = g./ml.) in 0·1M-sodium chloride at 546 mμ.

*Isolation of Glycogens.*—Unless otherwise stated, samples of glycogen had been isolated from the tissue by the classical Pflüger method involving digestion with 30% aqueous potassium hydroxide at 100°, followed by precipitation of the glycogen with ethanol and with acetic acid.[9] Commercial samples of glycogen from British Drug Houses Ltd. (I), and Nutritional Biochemicals Corporation, Ohio, U.S.A. (II), were also examined. Methylated horse-muscle glycogen was kindly provided by Dr. D. J. Bell.

## Results and Discussion

*Sedimentation Coefficients.*—Typical sedimentation data are shown in Table 1. It was apparent that for all the glycogens studied in detail, the sedimentation constant ($S_{20}$) was dependent on the concentration ($c$), and varied by about 10% for a 1% change in concentration. This is in general agreement with Larner, Ray, and Crandall's results,[10] but, whilst these authors suggested that $S_{20}$ was a function of $c^2$, our values were best

Table 1. *Typical sedimentation results.*

| | | $10^{13}S_{20}$ at $c$ (g./100 ml.) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Glycogen sample | Solvent | 1·0 | 0·75 | 0·50 | 0·25 | 0·16 | 0·125 | 0·08 | 0 (extrapol.) |
| *Ascaris lumbricoides* ... | 0·1M-NaCl | 47 | 47 | 47 | 48 | — | — | — | 48 |
| Brewer's yeast ..... | 0·1M-NaCl | 56 | — | 60 | 61 | — | 62 | — | 64 |
| ,, ..... | 1M-NaCl | 54 | — | — | — | — | — | — | — |
| ,, ..... | 0·2M-NaOH | 56 | 58 | 60 | 61 | 62 | — | 63 | 64 |
| Commercial, II ..... | 0·1M-NaCl | 65 | 67 | 69 | 71 | — | — | — | 73 |

represented by a linear function. The relations was expressed by $S_{20} = (S_{20})_0(1 - kc)$, where $(S_{20})_0$ is the value of $S_{20}$ at infinite dilution, and $c$ was expressed in g./100 ml. With the exception of the *Ascaris lumbricoides* glycogen (which was relatively concentration-independent; see Table 1), the average value of $k$ was $0{\cdot}10 \pm 0{\cdot}02$. Values of $(S_{20})_0$ for glycogens examined at only one concentration were therefore calculated from this value, and are shown in parentheses in the second and third columns of Table 2.

*Molecular Weight and its Distribution.*—Table 2 shows the results of the sedimentation measurements for the 23 samples examined. Typical sedimentation diagrams are shown in the Figure. Most samples proved to be polydisperse on ultracentrifugation. Diagrams *a* and *b* (for oyster and *Helix pomatia* glycogen) illustrate the type of Schlieren diagram observed for the most obviously polydisperse samples. This feature is unusual, although Polglase, Brown, and Smith [11] reported similar results for samples of human-liver glycogen. The amounts of main components quoted in the Table are only approximate as no attempt was made to correct for boundary anomaly effects.[12] For many samples, an extremely wide molecular-weight distribution was indicated; the leading sedimentation boundary

[7] Putzeys and Verhoeven, *Rec. Trav. chim.*, 1949, **68**, 817.
[8] Stetten, Katzen, and Stetten, *J. Biol. Chem.*, 1956, **222**, 587.
[9] Bell and Manners, *J.*, 1952, 3641; Manners and Archibald, *J.*, 1957, 2205.
[10] Larner, Ray, and Crandall, *J. Amer. Chem. Soc.*, 1956, **78**, 5890.
[11] Polglase, Brown, and Smith, *J. Biol. Chem.*, 1953, **199**, 105.
[12] See, *e.g.*, Trautman, Schumaker, Harrington, and Schachman, *J. Chem. Phys.*, 1954, **22**, 555.

was extremely asymmetric and reached nearly to the bottom of the cell after a short time of centrifugation. It was difficult to prove whether or not this leading boundary was a second component, and hence no attempt was made to estimate either its amount or its approximate sedimentation constant. Samples which showed this probable fast component are indicated by the symbol $S_{20}$(F) in the Table. In some other samples, a corresponding asymmetric lower molecular weight distribution was apparent. Again, no analysis of this was attempted and this is indicated by the symbol $S_{20}$(S) in Table 2.

TABLE 2. *Sedimentation results.*

| Glycogen sample | $10^{13}S_{20}$ of components [a] major | minor | Major component (%) | $dB/dx$ [b] | $10^{-6}M$ | $f/f_0$ [d] |
|---|---|---|---|---|---|---|
| | (a) *Mammalian livers* | | | | | |
| Cat I | 75 | F, S | — | 0·8 | 4·4 | — |
| ,, IV | 84 | F, S | — | — | 4·9 | — |
| ,, VI | (102) | F, S | — | 1·0 | 5·9 | — |
| Human (glycogen-storage disease) | (53) | (220) | 70 | 1·8 | 3·1 | — |
| Fœtal sheep | 110 | F | — | 1·1 | 6·4 | — |
| Fœtal pig | (49) | (11) | 70 | 0·8 | 2·9 | — |
| Rabbit II | 94 | — | 95+ | — | 5·5 | 1·7 |
| ,, (fructose-infused [e]) | (80) | F | — | 1·1 | 4·7 | — |
| ,, (galactose-infused [e]) | (153) | S | — | — | 9·0 | — |
| ,, (normal [e]) | (145) | F | — | 1·8 | 8·4 | — |
| | (b) *Mammalian muscles* | | | | | |
| Horse (methylated) | 23 | — | 95+ | — | 2·8 | 1·4 |
| Human | (85) | (20) | 85 | 0·8 | 4·9 | — |
| Rabbit I | 79 | — | 95+ | 0·7 | 4·6 | 1·9 |
| | (c) *Other glycogens* | | | | | |
| *Ascaris lumbricoides* | 48 | F | — | — | 2·8 | — |
| Brewer's yeast | 64 | — | 95+ | — | 3·7 | 2·0 |
| Commercial, I | 24 | — | 95+ | — | 0·7 | 1·9 |
| ,, II | 73 | — | 95+ | — | 4·0 | 1·7 |
| *Helix pomatia* II | (63) | (300, 7) | 80 | 0·9 | 3·6 | — |
| *Mytilus edulis* I | (93) | F | — | 0·9 | 5·4 | — |
| Oyster [e] | (45) | (90, F) | — | — | 2·6 | — |
| *Tetrahymena pyriformis* I | (69) | S | — | — | 4·0 | — |
| *Trichomonas foetus* I | (70) | S | — | — | 4·0 | — |
| *Trichomonas gallinae* I | (84) | S | — | — | 4·9 | — |

[a] For values in parentheses and meaning of F and S, see text. [b] Value for main component at $c$ (total) = 1·00 g./100 ml. [c] Molecular weight calculated from $M = \boldsymbol{R}T(S_{20})_0/(1 - \overline{V}\rho)D_m$. [d] Frictional ratio calculated from $f/f_0 = 10^{-8}[(1 - \overline{V}\rho)/D_m{}^2(S_{20})_0\overline{V}]^{1/3}$.

[e] Samples kindly supplied by Dr. M. Schlamowitz.

Diffusion measurements showed that for methylated horse muscle the diffusion coefficient ($D_m$) = $1·0 \times 10^{-7}$; for brewer's yeast glycogen, $D_m = 1·1 \times 10^{-7}$; for commercial glycogen I, $D_m = 2·0 \times 10^{-7}$; and for commercial glycogen II, $D_m = 1·1 \times 10^{-7}$ The molecular weights shown in Table 2 for the main components in the other samples are calculated by assuming a value of $1·1 \times 10^{-7}$ for $D_m$ in agreement with other workers.[2] All the molecular weights are in the range (3—9) $\times 10^6$, and, together with the values of the frictional ratio ($f/f_0$), are of the same order as those previously reported from sedimentation and diffusion measurements.[2,13] It should be noted, however, that the values for rabbit liver and muscle are considerably lower than those recently reported by Stetten, Katzen, and Stetten [8] (see below).

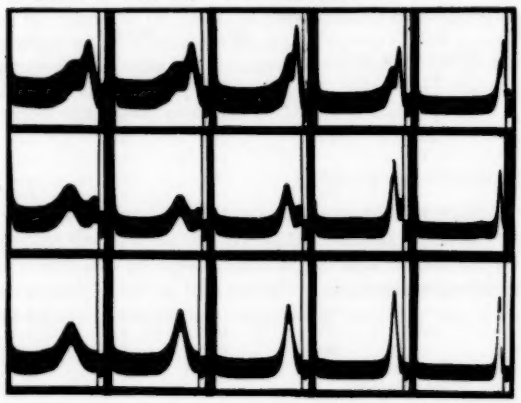
The values of ($dB/dx$) confirm qualitatively the extremely polymolecular nature of glycogen (cf. ref. 5) in agreement with the distributions evaluated by Larner and his

[13] Cori, *Makromol. Chem.*, 1956, **20**, 169.

co-workers.[10] Further, in agreement with these authors, mammalian-muscle glycogens appear to be less polymolecular than liver glycogens.

The polydisperse nature of most of the samples studied was confirmed by turbidimetric measurements. Although the molecular weight from these measurements is a true weight-average whilst that from sedimentation and diffusion is less well-defined,[14] the results from both these methods on a given polymolecular sample should be of the same order of magnitude. Polydispersity, particularly if it involves components of high molecular

*Typical sedimentation diagrams. For all samples, c = 1 g./100 ml.; solvent, 1·0M-sodium chloride; speed = 20,000 r.p.m. Movement of the peaks is from right to left. The figures in parentheses after the times indicate the angle of the Schlieren bar.*




*Oyster glycogen*: 8 (55°), 15 (45°), 18 (35°), 30 (30°), *and* 47 (25°) *min. after reaching full speed.*

Helix pomatia *glycogen*: 6 (65°) 14 (45°), 25 (45°) 37 (45°), *and* 50 (35°) *min. after reaching full speed.*

*Brewer's yeast glycogen*: 9 (65°), 17 (50°), 26 (45°), 37 (40°), *and* 52 (40°) *min. after reaching full speed.*

weight will cause disparities. Table 3 shows the results of light-scattering measurements on the ten samples which appeared to be the least obviously polydisperse on ultracentrifugation. For four of these, the agreement is reasonably good, indicating that they were only polymolecular, whilst the presence of $S_{20}$(F) in the other samples is convincingly illustrated

TABLE 3. *Light-scattering results.*

| Sample | Uncorr. $10^{-6}$M | Dissymmetry | $1/P_{90°}$ | Corr. $10^{-6}$M |
|---|---|---|---|---|
| *Liver glycogens* | | | | |
| Cat I | 10·5 | 1·48 | 1·30 | 13·6 |
| ,, IV | 8·8 | 1·85 | 1·52 | 13·4 |
| ,, VI | 12·8 | 1·67 | 1·40 | 17·9 |
| Rabbit II * | 6·9 | 1·20 | 1·13 | 7·8 |
| *Other glycogens* | | | | |
| *Ascaris lumbricoides* | 7·1 | 1·40 | 1·26 | 8·9 |
| Brewer's yeast * | 4·0 | 1·15 | 1·10 | 4·4 |
| Commercial, I | 1·7 | 1·19 | 1·12 | 1·9 |
| ,, II * | 4·9 | 1·15 | 1·10 | 5·4 |
| Rabbit muscle I * | 3·7 | 1·17 | 1·11 | 4·1 |
| *Tetrahymena pyriformis* I | 6·1 | 2·50 | 1·85 | 11·3 |

* Samples exhibiting no polydispersity.

by the higher turbidimetric molecular weight. It is therefore suggested that a given glycogen sample should be examined by both the sedimentation and the light-scattering method in order to prove unambiguously whether or not it is polydisperse. Without

[14] See, *e.g.*, Kinell and Rånby in "Advances in Colloid Science," Vol. III, Interscience, Publ. Inc., New York, 1950.

further investigations, it is not possible to decide whether polydispersity occurs in native glycogen in the tissue or is an artefact resulting from degradation during isolation. Polglase and his co-workers [11] consider that such variations occur naturally.

*Effect of Isolation Procedure on Molecular Weight.*—The classical Pflüger method involving digestion of tissue with 30% potassium hydroxide has often been criticised [15] on the assumption that alkaline degradation occurs. Table 4 shows the results for the determination of $S_{20}$ for glycogen samples isolated from the halves of two rabbit livers severally with boiling water and 30% aqueous potassium hydroxide. Within experimental error, $S_{20}$ is the same for all samples. It is concluded that, in the presence of air, the extent of degradation of glycogen by 30% potassium hydroxide solution at 100° is no greater than that which might be caused by boiling water. Similar results have been obtained by Staudinger,[16] and Bridgman [17] reported that glycogen extracted with cold trichloroacetic acid and hot alkali from two halves of a rabbit liver had a similar molecular weight. However, recent light-scattering work by Stetten, Katzen, and Stetten [8] has shown that if extraction with trichloroacetic acid is for a limited time at 0° the glycogen from rabbit liver has an average molecular weight of (11—80) $\times$ $10^6$ rather than the (2—6) $\times$ $10^6$ as in hot potassium hydroxide extractions. This suggests that it is difficult to avoid degradation during extraction, and that the molecular weights reported here and previously [2] may not be representative of " native " glycogen.

*Effect of Dilute Alkali and Acetic Acid.*—In contrast to the behaviour of hot 30% alkali, hot *dilute* alkali appears to degrade glycogen rapidly. Digestion of rabbit-liver glycogen in 8% aqueous sodium hydroxide at 100° for 1·5 hr. reduced $S_{20}$ from 86 to 57 $\times$ $10^{-13}$ c.g.s. units (see Table 4), and increased the polymolecularity (as shown by a broadening of the peak of the Schlieren pattern).

It has been suggested [18] that purification of glycogen by precipitation with glacial acetic acid may render it unsuitable for ultracentrifugal analysis. However, when rabbit-liver and brewer's yeast glycogens were reprecipitated with 80% acetic acid there was no change in the value of $S_{20}$ (see Table 4). Precipitation of glycogen by acetic acid does not, therefore, alter the hydrodynamic properties or cause degradation of glucosidic linkages to any appreciable extent.

TABLE 4. *Effect of isolation procedure on the sedimentation constant.*

| Sample | Method of isolation | $10^{13}S_{20}$ at $c$ = 1 g./100 ml. |
|---|---|---|
| Rabbit liver XII | Hot water | 85 |
| | 30% KOH at 100° | 86 |
| Rabbit liver XIII | Hot water | 76 |
| | 30% KOH | 83 |
| | 30% KOH + repptn. with AcOH | 83 |
| Rabbit liver IV | 30% KOH | 86 |
| | 30% KOH + 8% NaOH at 100° for 1½ hr. | 57 |
| Brewer's yeast | 30% KOH | 64 |
| | 30% KOH + repptn. with AcOH | 63 |

The authors thank Professor E. L. Hirst, F.R.S., for his interest in this work, and the Rockefeller Foundation for financial support, also the D.S.I.R. for a maintenance grant (to W. A. J. B.).

DEPARTMENT OF CHEMISTRY,
THE UNIVERSITY, EDINBURGH, 9. [*Received, August 12th*, 1957.]

[15] *E.g.*, Meyer and Jeanloz, *Helv. Chim. Acta*, 1943, **26**, 1784.
[16] Staudinger, *Makromol. Chem.*, 1948, **2**, 88.
[17] Bridgman, *J. Amer. Chem. Soc.*, 1942, **64**, 2349.
[18] Illingworth, Larner, and Cori, *J. Biol. Chem.*, 1952, **199**, 105.

XUM

## 139. *Raman Spectra of the Tetraiodogallate* ($GaI_4^-$) *and Tetraiodoindate* ($InI_4^-$) *Ions in Aqueous Solution.*

By L. A. Woodward and G. H. Singer.

An aqueous solution of gallium(III) iodide containing hydriodic acid gives four Raman frequencies, which are attributed to the $GaI_4^-$ ion of regular tetrahedral shape: $\nu_2(E) = 52$, $\nu_4(F_2) = 73$, $\nu_1(A_1) = 145$, and $\nu_3(F_2) = 222$ cm.$^{-1}$. A corresponding solution of indium(III) iodide containing hydriodic acid shows an analogous spectrum, attributed to the tetrahedral $InI_4^-$ ion: $\nu_2 = 42$, $\nu_4 = 58$, $\nu_1 = 139$, and $\nu_3 = 185$ cm.$^{-1}$. Comparisons are made with the frequencies of isoelectronic species.

Previous work[1,2] on the Raman spectra of the tetrachlorogallate ($GaCl_4^-$) and tetrabromogallate ($GaBr_4^-$) ions in aqueous solutions of the gallium(III) halide in presence of excess of the corresponding hydrogen halide has been extended to gallium(III) iodide (1·4 moles of $GaI_3$ per l.) containing excess of hydriodic acid (2·8M). An intense Raman spectrum, analogous in all respects to those of $GaCl_4^-$ and $GaBr_4^-$, was observed, whose characteristics are in Table 1. The spectrum is attributed to the $GaI_4^-$ ion.

Table 1. *Raman spectrum of the* $GaI_4^-$ *ion in aqueous solution.*

| $\Delta\nu$ (cm.$^{-1}$) | 52 | 73 | 145 | 222 |
|---|---|---|---|---|
| Intensity | Medium | Medium | Very strong | Weak |
| Appearance | Sharp | Sharp | Sharp | Diffuse |
| Polarization | Depolarized | Depolarized | Highly polarized | Depolarized |
| Assignment | $\nu_2(E)$ | $\nu_4(F_2)$ | $\nu_1(A_1)$ | $\nu_3(F_2)$ |

The regular decrease of frequencies in the series $GaCl_4^-$, $GaBr_4^-$, $GaI_4^-$ (Table 2), together with the number of the observed frequencies and the states of polarization, provide very strong evidence that all three species are of the same regular tetrahedral $XY_4$ shape (point group $T_d$).

Table 2. *Vibrational frequencies of tetrahalogenogallate ions.*

| | $\nu_2(E)$ | $\nu_4(F_2)$ | $\nu_1(A_1)$ | $\nu_3(F_2)$ | Ref. |
|---|---|---|---|---|---|
| $GaCl_4^-$ | 114 | 149 | 346 | 386 | 1 |
| $GaBr_4^-$ | 71 | 102 | 210 | 278 | 2 |
| $GaI_4^-$ | 52 | 73 | 145 | 222 | Present work |

As the Raman spectra of aqueous solutions of indium(III) bromide (1 mole of $InBr_3$ per l.) containing excess of hydrobromic acid (up to 6M) provide no evidence[3] for the presence of the $InBr_4^-$ ion, the tendency in aqueous solution to complex formation with bromide ions is less for $In^{3+}$ than for $Ga^{3+}$: only by extraction into an organic solvent

Table 3. *Raman spectrum of the* $InI_4^-$ *ion in aqueous solution.*

| $\Delta\nu$ (cm.$^{-1}$) | 42 | 58 | 139 | 185 |
|---|---|---|---|---|
| Intensity | Medium | Medium | Very strong | Medium |
| Appearance | Sharp | Sharp | Sharp | Diffuse |
| Polarization | Depolarized | Depolarized | Highly polarized | Depolarized |
| Assignment | $\nu_2(E)$ | $\nu_4(F_2)$ | $\nu_1(A_1)$ | $\nu_3(F_2)$ |

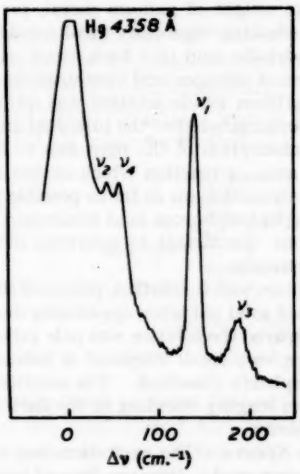
could the four-line Raman spectrum characteristic of the $InBr_4^-$ ion be obtained. With iodide ions the tendency to complex formation is expected to be stronger; we have now found that an aqueous solution of indium(III) iodide (1·0 mole of $InI_3$ per l.) containing

[1] Woodward and Nord, *J.*, 1956, 3721.
[2] *Idem*, *J.*, 1955, 2655.
[3] Woodward and Bill, *ibid.*, p. 1699.

excess of hydriodic acid (4M) gives an intense Raman spectrum (Table 3) entirely analogous to that reported above for $GaI_4^-$ and clearly attributable to the ion $InI_4^-$, which must be the predominant complex present in the solution.

The value of $\nu_2$ (42 cm.$^{-1}$) is amongst the lowest vibrational frequencies so far measured for any tetrahedral $XY_4$ species. The microphotometer trace of the spectrum reproduced in the Figure shows that, despite their close proximity to the relatively very intense primary line (Hg 4358 Å), both $\nu_2$ and $\nu_4$ are well resolved. As is generally found, they appear even more distinct when the original photograph is examined visually.

As $In^{3+}$ shows less tendency to form halide complexes than does $Ga^{3+}$, it has not so far been possible to obtain the Raman spectrum of the $InCl_4^-$ ion, so a full comparison of the kind made for gallium in Table 2 cannot be presented; but the frequencies ascribed to




*Raman spectrum of the* $InI_4^-$ *ion in aqueous solution, excited by* Hg 4358 Å *radiation.*

$InI_4^-$ in Table 3 clearly bear the same kind of relation to those[3] of $InBr_4^-$ ($\nu_2 = 55$; $\nu_4 = 79$; $\nu_1 = 197$; $\nu_3 = 239$ cm.$^{-1}$) as do the frequencies of $GaI_4^-$ to those of $GaBr_4^-$ (Table 2).

The $GaI_4^-$ ion is isoelectronic with the doubly-negative $ZnI_4^{2-}$ ion and with the neutral $GeI_4$ molecule. The $InI_4^-$ ion likewise forms the middle member of an isoelectronic triad with $CdI_4^{2-}$ and $SnI_4$. The observed Raman frequencies (cm.$^{-1}$) are compared in Table 4.

TABLE 4. *Vibrational frequencies of Isoelectronic Triads.*

| | $\nu_2$ | $\nu_4$ | $\nu_1$ | $\nu_3$ | $10^{-5}k$ | Ref. |
|---|---|---|---|---|---|---|
| $ZnI_4^{2-}$ ..... | 44 | 62 | 122 | 170 | 1·11 | 4 |
| $GaI_4^-$ ..... | 52 | 73 | 145 | 222 | 1·57 | Present work |
| $GeI_4$ ..... | 60 | 80 | 159 | 264 | 1·80 | 5 |
| $CdI_4^{2-}$ ..... | 36 | 44 | 117 | 145 | 1·02 | 6 |
| $InI_4^-$ ..... | 42 | 58 | 139 | 185 | 1·44 | Present work |
| $SnI_4$ ..... | 47 | 63 | 149 | 216 | 1·66 | 5 |

In both triads there is a progressive increase of all four fundamental frequencies as the atomic number of the central metal atom increases. As regards the totally symmetrical " breathing " frequencies $\nu_1$, this means that the stretching force constant $k$ of the metal–iodine bond increases in the same order. The values of $10^{-5}k$ (dynes per cm.), calculated

[4] Delwaulle, *Compt. rend.*, 1955, **240**, 2132.
[5] Stammreich, Forneris, and Tavares, *J. Chem. Phys.*, 1956, **25**, 1275.
[6] Delwaulle, François, and Wiemann, *Compt. rend.*, 1939, **208**, 184; Rolfe, Sheppard, and Woodward, *Trans. Faraday Soc.*, 1954, **50**, 1275.

on the basis of a simple valency-force field, are included in Table 4. For both triads the value of $k$ (or of $\nu_1$, from which $k$ is derived) for the singly-negative ion is not midway between the corresponding values for the other two isoelectronic species. In fact the increase in passing from the doubly to the singly charged ion is greater than that in passing from the latter to the neutral molecule. This non-linear variation of $k$ with the atomic number of the central atom, which is qualitatively the same as for other sets[1,7,8] of isoelectronic species of the regular tetrahedral $XY_4$ type, will be discussed subsequently.

## Experimental

*Preparation of Solutions.*—The solution of gallium iodide was prepared by dissolving the appropriate weight of gallium metal, previously reduced to small particles by adding warm water and shaking vigorously until resolidification occurred, in a known quantity of constant-boiling hydriodic acid in a flask fitted with a Bunsen valve. The acid had been redistilled in a current of nitrogen and contained some hypophosphorous acid to keep it colourless. The resulting gallium iodide solution was quite clear and showed no colour due to free iodine. It had been anticipated that the principal experimental difficulty in obtaining the Raman spectra would be absorption of the light due to liberation of iodine by the oxidation of the excess of hydriodic acid—a reaction which occurs readily, especially under intense illumination. Care was taken to exclude air as far as possible from the Raman vessel containing the solution. The trace of hypophosphorous acid minimized the amount of free iodine formed, and only a slight iodine colour, insufficient to interfere, developed at the free surface of the solution during the Raman exposures.

The indium iodide solution, prepared similarly, had to be filtered to remove a small quantity of suspended solid particles, apparently due to reaction with the trace of hypophosphorous acid. As first prepared the solution was pale yellow. Before each Raman exposure it was decolorised by adding a very small fragment of indium metal (which evolved hydrogen) and waiting until it was completely dissolved. The solution coloured during illumination in the Raman source, and even on lengthy standing in the dark; good Raman spectra (see Figure) were nevertheless obtained easily.

*Raman Spectra.*—The excitation was by means of a " Toronto arc," the blue mercury line (4358 Å) being used. Primary lines of lower wavelength were reduced in intensity by a sodium nitrite filter. Qualitative determinations of the states of polarization of the Raman lines were made by the method of polarized incident light, successive exposures being taken with suitable Polaroid cylinders surrounding the Raman tube. The volume of solution was in each case about 19 ml. In view of the low $\Delta\nu$ values a Hilger type E.612 two-prism spectrograph with $f/5{\cdot}6$ camera was used; a higher dispersion and resolving power was thus obtained than in the work on the chloro- and bromo-complex ions. The frequency shifts were measured in the usual way with an iron-arc spectrum as standard. The values given are correct to within $\pm 2$ cm.$^{-1}$; for the sharper lines the accuracy is probably better. The photographic plates used were Kodak Special Scientific, emulsion type Oa, sensitivity G. The four-line spectra were obtained with exposure times of only 5 min. The intensity of Raman scattering by the ions $GaI_4^-$ and $InI_4^-$ is evidently very great. Longer times showed no further features.

The Inorganic Chemistry Laboratory, Oxford. [*Received, August 13th*, 1957.]

[7] Woodward and Roberts, *J.*, 1956, 1170.
[8] *Idem, Trans. Faraday Soc.*, 1956, **52**, 1458.

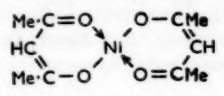
## 140. *Tetrahedral Nickel*(II) *Complexes and the Factors Determining Their Formation. Part I. Bistriphenylphosphine Nickel*(II) *Compounds.*

By L. M. VENANZI.

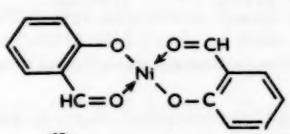
The compounds $(Ph_3P)_2NiX_2$ (X = Cl, Br, I, $NO_3$, and SCN) have been prepared and their properties studied. The chloro- and iodo-, and presumably also the bromo- and nitrato-complexes, have tetrahedral structure, and $\mu_{eff.}$'s of about 3 B.M. The thiocyanato-complex is diamagnetic and has *trans*-square planar structure.

The formation of tetrahedral nickel(II) complexes is discussed in terms of ligand-field theory.

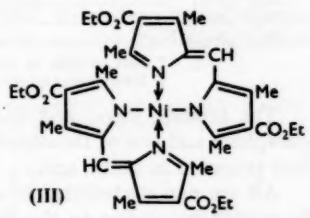
CONTRARY to general belief, tetrahedral complexes of nickel(II) are rather uncommon. This structure has been assigned to many such compounds, *e.g.*, bisacetylacetonenickel (I) ($\mu_{eff.}$ = 3·2 B.M.),[1,2] dehydrated bis-salicylaldehydenickel (II) (paramagnetic),[3] bis(diethyl-3 : 3′ : 5 : 5′-tetramethylpyrromethene-4 : 4′-dicarboxylate)nickel (III) ($\mu_{eff.}$ = 3·2 B.M.),[4] and bistriethylphosphinedinitratonickel, $(Et_3P)_2Ni(NO_3)_2$ ($\mu_{eff.}$ = 3·10 B.M.).[5]




(I)




(II)




(III)

No unambiguous evidence, however, has been advanced to show that any of these is tetrahedral. Bisacetylacetonenickel is trimeric in the solid state,[6] and the fact that it is monomeric in pentyl benzoate [7] is not very significant because the latter is a donor solvent. Dehydrated bis-salicylaldehydenickel has an *X*-ray powder pattern different from that of bis-salicylaldehydecopper, which is said to have square planar structure,[3] and very similar to that of the dehydrated zinc complex, the structure of which is not known. Moreover, the nickel and the zinc complex appeared to be incompletely dehydrated.[3]

The pyrromethene complex (III) has been ascribed tetrahedral structure on the basis of its paramagnetism, and the fact that calculations of van der Waals radii for the molecule show serious overlap of the α-methyl groups.[4] No molecular-weight determination, however, has been reported, and the presence of other potential donor groups in the molecule casts doubt on the validity of the conclusions.

Bistriethylphosphinedinitratonickel, $(Et_3P)_2Ni(NO_3)_2$, has always been considered most probably to be tetrahedral. It is monomeric in benzene and has a high electric dipole moment (8·85 D).[8] The magnetic moment in solutions of non-donor solvents, however, has not been measured, and Nyholm has pointed out that stereochemical arrangements other than tetrahedral can also be postulated for such a compound.[9,10]

At the beginning of the present investigation the only well-established cases of nickel(II)

[1] Mellor and Craig, *J. Proc. Roy. Soc. N.S.W.*, 1940, **74**, 475.
[2] Basolo and Matoush, *J. Amer. Chem. Soc.*, 1953, **75**, 5663.
[3] Curtiss *et al.*, *Acta Cryst.*, 1952, **5**, 388.
[4] Mellor and Lockwood, *J. Proc. Roy. Soc. N.S.W.*, 1940, **74**, 141.
[5] Asmussen *et al.*, *Acta Chem. Scand.*, 1955, **9**, 1391.
[6] Bullen, *Nature*, 1956, **177**, 537.
[7] Gach, *Sitzungsber. Akad. Wiss. Wien, Mat.-Naturwiss. Classe*, 1899, IIb, **108**, 773.
[8] Jensen, *Z. anorg. Chem.*, 1936, **229**, 265.
[9] Nyholm, *Chem. Revs.*, 1953, **53**, 263.
[10] Nyholm, Report to the 10th Solvay Council, Brussels, 1956, 225.

ions with tetrahedral co-ordination were: (*a*) some sodium silicate glasses containing nickel(II),[11] and (*b*) $NiCr_2O_4$, which has a spinel structure, with the nickel atoms in the tetrahedral holes of the oxygen lattice.[11a]

In an attempt to isolate some tetrahedral complexes of nickel(II), the most promising set of compounds appeared to be that given by substituted tertiary phosphines.

Jensen [8] reported that, during the preparation of $(Et_3P)_2Ni(NO_3)_2$, and more markedly during the preparation of $(Et_2PhP)_2Ni(NO_3)_2$, a transient red colour appears, which he attributed to the formation of an intermediate square planar complex. It was therefore of interest to study the structure of the compounds of the type $(Ph_3P)_2NiX_2$ (X = Cl, Br, and I) described by Reppe and Schweckendiek [12] and by Yamamoto,[13] which are blue, dark green, and brown, respectively. The properties of these and two other compounds are listed in the Table.

*Colour, decomposition point, electric dipole moment, and magnetic moment of triphenylphosphine complexes of nickel(II).*

| Compound | Colour | Decomp. point | $\mu$ (D) | $\mu_{eff.}$ (B.M.) |
|---|---|---|---|---|
| $(Ph_3P)_2NiCl_2$ | Blue | 247—250° | — * | 3·07 |
| $(Ph_3P)_2NiBr_2$ | Dark green | 222—225 | 5·9 | 2·97 |
| $(Ph_3P)_2NiI_2$ | Brown | 218—220 | 8·5 | 2·92 |
| $(Ph_3P)_2Ni(NO_3)_2$ † | Green | 224—227 | — * | 3·04 |
| $(Ph_3P)_2Ni(SCN)_2$ † | Red | 217—218 | <3 | diamag. |

* Not soluble in non-donor solvents suitable for such measurements.
† New compounds.

The bromo-, iodo-, and thiocyanato-derivatives were prepared from 2 equiv. of the phosphine and one of the nickel salt in butanol. The chloro- and nitrato-derivatives are best prepared in acetic acid.

All are non-electrolytes in nitrobenzene. Molecular-weight determinations could not be carried out owing to the high values and the low solubility in non-donor solvents. *X*-Ray structural work showed that solid $(Ph_3P)_2NiCl_2$ and $(Ph_3P)_2NiI_2$ are monomeric.[14] This work, which will be reported later, also shows that the chloro-complex is tetrahedral, and that the iodo-complex definitely is not *cis*-planar. This, in conjunction with dipole-moment measurements, leads to the conclusion that $(Ph_3P)_2NiI_2$ also is tetrahedral; [9] by analogy $(Ph_3P)_2NiBr_2$ is as well.

The thiocyanato-complex, $(Ph_3P)_2Ni(SCN)_2$, because of its diamagnetism and low dipole moment, is attributed *trans*-square planar structure.

The change in stereochemistry and bond type on going from the halides to the thiocyanate is in keeping with the known empirical relation between magnetism and structure for this class of compound.[1]

One remarkable feature is the lability of these complexes; they are not formed in the presence of, and are decomposed by, the lower alcohols, thus explaining Jensen's failure to prepare them, and are readily decomposed by all donor solvents.

Repeated attempts to prepare the compounds $(Ph_3P)_2NiX_2$ (X = F, $NO_2$, and CN) failed. Triphenylarsine and triphenylstibine also failed to form complexes, both in butanol and in acetic acid. The complexes are not formed even by tri-*p*-tolyl-, tri-*p*-anisyl-, and tri-*p*-chlorophenyl-phosphine. Failure to isolate complexes with triphenylarsine and triphenylstibine is not surprising in view of the lability of the triethylarsine complexes of nickel(II),[8] but it is difficult to account for the fact that *p*-substituted triphenylphosphines should not co-ordinate.

The rare occurrence of tetrahedral, paramagnetic nickel(II) complexes cannot be explained in terms of valence-bond theory. Overlap integral calculations indicate that

[11] Weil, Report to the 10th Solvay Council, Brussels, 1956, 419.
[11a] Dunitz and Orgel, *J. Phys. Chem. Solids*, 1957, **3**, 20.
[12] Reppe and Schweckendiek, *Annalen*, 1948, **560**, 104.
[13] Yamamoto, *Bull. Chem. Soc. Japan*, 1954, **27**, 501.
[14] Garton, Powell, and Venanzi, unpublished observations.

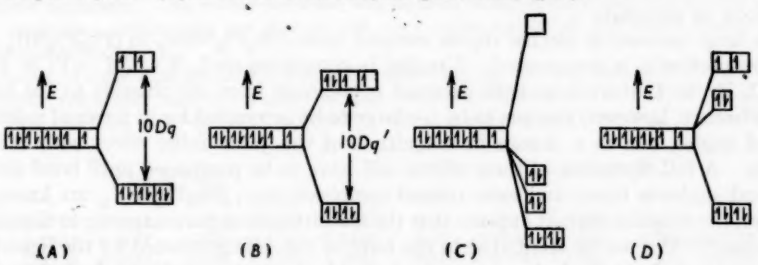
bonds involving $4s4p^3$ or $4s4p^34d^2$ hybridisation should be of comparable strength.[15] It appears, instead, that most paramagnetic nickel(II) complexes have a strong tendency to become octahedral. This is true even of the paramagnetic complexes $[NiX_4]^{2-}$ where six-co-ordination is attained by polymerisation: *e.g.*, $K_2[NiF_4]$,[16] which can be represented as $K_2[Ni(\frac{1}{2}F)_4F_2]$.

A satisfactory explanation is supplied by the application of ligand-field theory to $d^8$ systems. The splitting of the *d*-levels in the field generated by the ligands for various stereochemical arrangements is given in the Figure. It can be seen that in the case of a cubic (octahedral) field the crystal-field stabilisation energy is equal to 12 *Dq*, while that for a tetrahedral field is equal to 8 *Dq'*.[17] To get a rough idea of the difference in crystal-field stabilisation energy between a cubic and a tetrahedral field, let us assume that, for a given ligand, *e.g.*, ethylenediamine, the *Dq* values are the same for the two fields (this is probably not the case, as we shall see later, but it will be a useful initial approximation).

The *Dq* value[17] for the complex $[en_3Ni]^{2+}$ is 1160 cm.$^{-1}$; the crystal-field stabilisation energy is then 13,920 cm.$^{-1}$. That for the hypothetical $[en_2Ni]^{2+}$ (tetrahedral) is then 9640 cm.$^{-1}$, and the difference, 4280 cm.$^{-1}$, corresponds to about 14 kcal.

There are no data from which to check these assumptions about *Dq* for tetrahedral nickel(II) complexes, and only meagre information about the values for tetrahedral complexes of other bivalent metals but, in general, it appears that, for a given ligand, the *Dq* values are only about one-half to two-thirds of those found in octahedral complexes.[18] The causes of this effect have been discussed by Orgel.[19]

d-*Orbital splitting due to the ligand field in* $d^8$ *systems.* (*A*), *Regular octahedral field* (*crystal-field stabilisation energy* 12 *Dq*). (*B*), *Regular tetrahedral field* (*crystal-field stabilisation energy* 8 *Dq'*). (*C*), *Square planar field.* (*D*), *Distorted tetrahedral field* (*Jahn–Teller effect*).




Assuming that the above generalisation is valid also in the case of nickel(II) complexes, one arrives at a value of about 500 cm.$^{-1}$ for the *Dq* value of the tetrahedral $[en_2Ni]^{2+}$ ion. The crystal-field stabilisation energy would then be 4000 cm.$^{-1}$, and the energy difference between a cubic and a tetrahedral field about 10,000 cm.$^{-1}$, corresponding to about 30 kcal. It is then reasonable to assume that the energy difference between the two fields will be between 15 and 30 kcal., and this would account, to a large extent, for the rare occurrence of tetrahedral nickel(II) complexes.*

The magnitude of the *Dq* values in the complexes $(Ph_3P)_2NiX_2$ is unknown, but they should not differ significantly from those calculated above.

Several authors [11a,20,21] have pointed out, however, that the Jahn–Teller effect will

* Ballhausen (*Dansk Mat. Fys. Medd.*, 1954, **29**, No. 4) showed that on a simple electrostatic basis *Dq* (tetrahedron) = $\frac{4}{9}$*Dq* (octahedron) for complexes of the same ligand, the same interatomic distances in both fields being assumed.

[15] Craig *et al.*, *J.*, 1954, 332.
[16] Balz and Plieth, *Z. Elektrochem.*, 1955, **59**, 545.
[17] Orgel, Report to the 10th Solvay Council, Brussels, 1956, p. 289.
[18] Orgel, *J. Chem. Phys.*, 1955, **23**, 1004.
[19] *Idem*, *ibid.*, p. 1819.
[20] Jörgensen, Report to the 10th Solvay Council, Brussels, 1956, 387.
[21] Owen, Thesis, Oxford, 1953.

XUM

operate in tetrahedral complexes of nickel(II). Ligand-field theory predicts that in a tetrahedral field the five-fold degenerate orbital levels of the single *d*-electron will be split into an upper triplet and a lower doublet. The eight *d*-electrons of nickel(II) fill these levels in the appropriate energy order consistent with Pauli's principle and Hund's rule which gives spin $S = 1$ (see Figure). There are then four electrons in the lower doublet and four in the upper triplet, and the energy of the system can be lowered by a Jahn–Teller distortion of the tetrahedron.[11a, 20, 21] This can be seen by the following argument: if the ligands are such that the tetrahedron has a two-fold axis of symmetry, a " stretching " along this axis will split the upper triplet into a lower singlet and an upper doublet, the centre of gravity of the system remaining unchanged. This splitting will be inverted if the tetrahedron is " flattened ". In the case of a complex $L_2NiX_2$ a " stretching " will reduce the LNiL and XNiX angles, and a " flattening " will increase these angles; the latter distortion will make the complex approach a square planar configuration.

With either of these distortions the energy of the seven electrons will be approximately unchanged, but that of the eighth electron will be lower if the tetrahedron is " stretched ". It is therefore to be expected that the lowest energy of the system will be obtained if the tetrahedron is " stretched ". This distortion, however, is not expected to be large, but it has been observed in $NiCr_2O_4$.[11a]

Asmussen *et al.*[5] find that $(Et_3P)_2Ni(NO_3)_2$ has $\mu_{eff.} = 3{\cdot}10$ B.M. Nyholm,[9] discussing the stereochemistry and magnetism of this compound, points out that a regular tetrahedral structure would give rise to a large orbital contribution to the magnetic moment, and attributes the small magnetic moment to the perturbing effect of the asymmetric field which may cause further splitting of the triplet. This splitting need not be attributed to the asymmetric field because the Jahn–Teller effect should operate in all tetrahedral complexes of nickel(II).

The large increase in electric dipole moment from $(Ph_3P)_2NiBr_2$ to $(Ph_3P)_2NiI_2$ (5·9 to 8·5 D, respectively) is unexpected. Usually, in complexes *cis*-$L_2MX_2$ (M = Pt or Pd, and X = Cl, Br, or I) there is a slight decrease in moment from the chloride to the iodide.[22] This difference, however, appears to be too large to be accounted for in terms of a difference in bond angles, due to a change in magnitude of the Jahn–Teller effect with change of halogen. A full discussion of these effects will have to be postponed until bond distances and bond angles in these, and some related complexes, *e.g.*, $(Ph_3P)_2ZnX_2$, are known.

From the available data it appears that the transition from paramagnetic to diamagnetic complexes [1, 17, 19] must be attributed to the force of the field generated by the ligands, and the formation of tetrahedral compounds, instead of paramagnetic octahedral ones, will occur only when the ligands do not have enough perturbing power to cause " spin pairing " and when a tetrahedral arrangement is forced by the steric requirements of the ligands.

## Experimental

*Bistriphenylphosphinedichloronickel.*—A solution of nickel chloride hexahydrate (2·38 g., 0·01 mole) in water (2 c.c.) was diluted with glacial acetic acid (50 c.c.), and triphenylphosphine (5·25 g., 0·02 mole) in glacial acetic acid (25 c.c.) added. The olive-green microcrystalline precipitate, when kept in contact with its mother-liquor for 24 hr., gave dark blue crystals which were filtered off, washed with glacial acetic acid, and dried in a vacuum desiccator ($H_2SO_4$; KOH); yield 84% (Found: C, 66·0; H, 4·7. Calc. for $C_{36}H_{30}Cl_2NiP_2$: C, 66·1; H, 4·6%).

*Bistriphenylphosphinedibromonickel.*—Triphenylphosphine (10·49 g., 0·04 mole) in boiling butanol (100 c.c.) was added to a solution of nickel bromide trihydrate (5·45 g., 0·02 mole) in boiling butanol (100 c.c.). On cooling, the pure product separated in well-formed crystals (72%) (Found: C, 58·25; H, 4·3. Calc. for $C_{36}H_{30}Br_2NiP_2$: C, 58·2; H, 4·1%).

*Bistriphenylphosphinedi-iodonickel.*—Nickel nitrate hexahydrate (2·91 g., 0·01 mole) in butanol (150 c.c.) was refluxed for 2 hr. with finely powdered potassium iodide (5 g., 0·03 mole). The mixture was cooled, and the solution filtered, heated to boiling, and added to a boiling

[22] Jensen, *Z. anorg. Chem.*, 1936, **229**, 225.

solution of triphenylphosphine (5·25 g., 0·02 mole) in butanol (50 c.c.). On slow cooling the product separated in thick plates (64%) (Found: C, 51·9; H, 3·8. Calc. for $C_{36}H_{30}I_2NiP_2$: C, 51·65; H, 3·6%).

*Bistriphenylphosphinedinitratonickel.*—This *complex* (93%) was prepared analogously to the chloro-complex (Found: C, 63·1; H, 4·5; N, 4·2. $C_{36}H_{30}O_6N_2NiP_2$ requires C, 61·2; H, 4·3; N, 4·0%).

*Bistriphenylphosphinedithiocyanatonickel.*—This *complex* (76%) was prepared analogously to the iodo-complex, from nickel nitrate, potassium thiocyanate, and triphenylphosphine (Found: C, 65·4; H, 4·4; N, 3·8. $C_{38}H_{30}N_2S_2P_2$ requires C, 64·25; H, 4·2; N, 4·0%).

*Conductance Measurements.*—These were done with a $10^{-3}$M-solution of the complex in nitrobenzene, a Type E 7566 Mullard conductivity bridge being used. All the compounds were non-electrolytes.

*Electric Dipole-moment Measurements.*—The moments were determined by measuring the dielectric constants and specific volumes of benzene solutions at 25°, the small-scale technique described by Everard and Sutton [23] being used with the heterodyne beat capacitance meter described by Hill and Sutton.[24] The meter was calibrated by assuming the value 2·2727 for the dielectric constant of benzene at 25°.[25] The pyknometer was calibrated with air-free distilled water.

The dipole moments were evaluated by the method of Everard, Hill, and Sutton,[26] so that no allowance was made for atom polarisation except that implicit in using $[R]_D$ as the distortion polarisation. Since the compounds are highly coloured and dissociate in strong light, it was impossible to measure the refractive index of the solutions. The molar refraction $[R]_D$ was evaluated from tables. The values used are quoted.

Other methods of calculating the slope, $\alpha$, of the $\varepsilon$–$w$ graphs, *e.g.*, that of Smith and Cleverdon,[27] give moments which agree with those obtained from Everard, Hill, and Sutton's method within the errors quoted. Jensen's approximate formula [28] was also used to evaluate the dipole moments. The values obtained will be seen to agree fairly well with those from the other methods. Differences are due to the very large values of $P_E$ which make Jensen's assumption dubious.

Benzene of analytical grade was purified as described by Hill and Sutton.[29]

Atomic refraction values: phenyl = 25·8 (benzene = 26·18, H = 1·10); [30] P = 9·14; [31] Ni = 18·8 [$Ni(CO)_4$ = 37·3,[32] CO = 4·63 [30]]; Br = 8·865; I = 13·900.[30]

| $(Ph_3P)_2NiBr_2$ | | | | | | $(Ph_3P)_2NiI_2$ | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $10^4w_2$ | $\varepsilon$ | $v$ | $10^4w_2$ | $\varepsilon$ | $v$ | $10^4w_2$ | $\varepsilon$ | $v$ | $10^4w_2$ | $\varepsilon$ | $v$ |
| 0 | 2·2727 | 1·1446 | 4·768 | 2·2760 | 1·1443 | 0 | 2·2727 | 1·1446 | 2·577 | — | 1·1444 |
| 3·864 | 2·2754 | 1·1445 | 5·688 | 2·2769 | 1·1443 | 3·385 | 2·2764 | 1·1442 | 4·856 | 2·2784 | 1·1442 |
| 2·451 | 2·2745 | 1·1445 | 4·933 | 2·2765 | 1·1443 | 5·818 | 2·2794 | 1·1442 | 4·856 | 2·2784 | 1·1442 |
| | | | | | | | | | 2·587 | 2·2759 | — |

$\varepsilon = 2·2727 + 7·366w_2$
$v = 1·1446 - 0·589w_2$
$P_T = 906·9$ c.c.
$P_E = 205·4$ c.c.
$\mu = 5·9 \pm 0·3$ D

$\varepsilon = 2·2728 + 11·511w_2$
$v = 1·1445 - 0·734w_2$
$P_T = 1710·7$ c.c.
$P_E = 215·4$ c.c.
$\mu = 8·5 \pm 0·3$ D

Calc. from Jensen's formula:

$\mu = 6·4 \pm 0·3$ D

$\mu = 8·7 \pm 0·3$ D

Bistriphenylphosphinedithiocyanatonickel is probably non-polar, since its total polarisation is of the order of 200—250 c.c. and its electron polarisation should be about 210 c.c. The

[23] Everard and Sutton, *J.*, 1951, 16.
[24] Hill and Sutton, *J.*, 1953, 1482.
[25] Hartshorn and Oliver, *Proc. Roy. Soc.*, 1929, *A*, **123**, 664.
[26] Everard, Hill, and Sutton, *Trans. Faraday Soc.*, 1950, **46**, 417.
[27] Smith and Cleverdon, *ibid.*, 1949, **45**, 109.
[28] Jensen, *Acta Chem. Scand.*, 1949, **3**, 474.
[29] Hill and Sutton, *J.*, 1949, 746.
[30] Landolt-Börnstein's Tabellen, 1923, Vol. 2.
[31] Jones *et al.*, *J. Phys. Chem.*, 1933, **37**, 583.
[32] Bentley and Sutton, *Nature*, 1932, **130**, 314.

XUM

combination of low polarity and small molecular solubility made it impossible to measure the dipole moment, which is certainly less than 3 D:

| $10^6w_2$ | $\epsilon_{12}$ | |
|---|---|---|
| *ca.* 150 | 2·2731 | (satd. soln.) |

$_TP_\infty$ = 200—250 c.c.
$_BP_\infty$ = *ca.* 210 c.c.

*Magnetic-moment Measurements.*—These were done by use of a Gouy-type balance on finely powdered solids at 293° K and 90° K, and in the case of $(Ph_3P)_2NiBr_2$ and $(Ph_3P)_2NiI_2$ also at 373° K. The $\mu_{eff.}$'s were calculated from the values of the susceptibility at 90° K.

The author thanks Messrs. Albright and Wilson Ltd. for a generous gift of triphenylphosphine, Drs. J. Owen and L. E. Sutton for useful discussion, Mr. F. R. McKim for the measurements of magnetic susceptibilities, and Mr. C. M. Bax for the measurements of electric dipole moments. The present work was carried out during the tenure of an I.C.I. Fellowship.

INORGANIC CHEMISTRY LABORATORY,
SOUTH PARKS ROAD, OXFORD.

[*Received, September 2nd,* 1957.]

## 141. *The Structure of Laminarin. Part I. The Main Polymeric Linkage.*

By STANLEY PEAT, W. J. WHELAN, and H. G. LAWLEY.

The linkages in insoluble and soluble laminarin have been analysed by the method of partial hydrolysis. It is confirmed that the principal linkage is of the 1 : 3-type, between β-D-glucopyranose residues. The presence of other (minor) structural features in both forms of the polysaccharide is indicated. Some properties of the new sugars, laminari-triose, -tetraose, and -pentaose are reported.

THE polysaccharide laminarin is a reserve carbohydrate of the sublittoral brown algae (Phaeophyceae) and occurs principally in the *Laminariae*, the species from which most investigators have obtained their material.[1-5] Two types of laminarin are recognised; the water-insoluble laminarin, which is precipitated spontaneously from an aqueous acid extract of the weed,[6] and the soluble form, which separates from solution only on the addition of a precipitant, such as ethanol.[7,8] Both forms are reported to consist entirely of D-glucose residues [8-10] and no clear-cut differences in structure have been established.[8,9]

The character of the main, if not the only, polymeric linkage in insoluble laminarin was established first by Barry,[10] who isolated 2 : 4 : 6-tri-*O*-methyl-D-glucose in large yield from the hydrolytic products of the methylated polysaccharide. The chain-forming 1 : 3-linkage probably has the β-configuration because of the negative optical rotation of the polysaccharide and its derivatives.[8-11] Later workers [8,9] isolated the same trimethyl sugar together with smaller amounts of 2 : 3 : 4 : 6-tetra-, 2 : 6-di-, and 4 : 6-di-*O*-methyl-glucoses from both forms of methylated laminarin. Judgment on the origin of the dimethyl sugars was reserved since experiments showed that these same substances could arise by acid treatment of the trimethyl sugar. Accordingly, both forms of laminarin were depicted as linear chains of β-1 : 3-linked glucose residues, the proportion of tetramethylglucose obtained suggesting a chain length of about 20 glucose units in each case. Determination of the molecular weight by other methods gave results which were discordant among themselves and which did not agree with the estimate made by

[1] Black, *J. Soc. Chem. Ind.*, 1948, **67**, 165, 169, 172.
[2] Black, *Nature*, 1948, **161**, 174.
[3] Black, *J. Mar. Biol. Assoc. U.K.*, 1950, **29**, 45.
[4] Black, *J. Soc. Chem. Ind.*, 1950, **69**, 161.
[5] Black and Dewar, *J. Mar. Biol. Assoc. U.K.*, 1949, **28**, 673, 687.
[6] Barry, *Sci. Proc. Roy. Dublin Soc.*, 1938, **21**, 615.
[7] Black, Cornhill, Dewar, and Woodward, *J. Appl. Chem.*, 1951, **1**, 505.
[8] Percival and Ross, *J.*, 1951, 720.
[9] Connell, Hirst, and Percival, *J.*, 1950, 3494.
[10] Barry, *Sci. Proc. Roy. Dublin Soc.*, 1939, **22**, 59.
[11] Bächli and Percival, *J.*, 1952, 1243.

methylation assay.[8,9] Confirmatory evidence of the polysaccharide structure was provided by the isolation of a disaccharide (laminaribiose) from enzymic and acidic hydrolysates of insoluble laminarin.[11,12] Chemical synthesis[11,13] showed this to be 3-*O*-β-D-glucopyranosyl-D-glucose. The resistance of laminarin to periodate oxidation[14,15] is also consistent with 1 : 3-bonding and the supposed β-configuration of the linkage was confirmed by the hydrolytic action of specific β-glucosidases on laminarin.[16-18]

Various hypotheses have been advanced to explain the different physical properties of the two forms of laminarin[6,10,19,20] but detailed structural investigation has revealed no chemical difference except in regard to its reducing action towards alkaline hypoiodite.[8,9] Soluble laminarin has a higher weight-average molecular weight than the insoluble form but this is not believed to be the sole cause of the different solubilities.[21] As a result of physical and chemical investigations Broatch and Greenwood[22] have recently concluded that laminarin (of unspecified source) has a branched molecule. This is in line with our preliminary report[23] that β-1 : 6-links, which may represent points of branching, are present in both forms of laminarin.

Our interest in laminarin arose from the need to obtain the series of β-1 : 3-linked glucose oligosaccharides (laminaridextrins) as reference compounds. These substances would be the components of a partial acid hydrolysate of laminarin, if it is constituted as described above, and should be capable of isolation by charcoal–chromatographic fractionation. When this procedure was carried out on a sample of insoluble laminarin it at once became obvious that although glucose and the laminaridextrins were the main components of the mixture, other products were present in amounts which suggested that they represented significant and previously unrecognised features of the laminarin molecule. Accordingly, detailed investigations of both forms of the polysaccharide were undertaken by the method of linkage analysis.[24] For convenience of presentation, this paper describes the characterisation of the main hydrolysis components. Part II (following paper) deals in detail with the minor components.

*Insoluble Laminarin.*—The polysaccharide (22 g.) was partly hydrolysed in hot 0·33N-sulphuric acid and the products fractionated on charcoal–Celite. The monosaccharide fraction consisted mainly of glucose (3·62 g.), characterised as the β-penta-acetate, together with mannitol.[25] The higher-molecular weight groups were similar mixtures of major and minor conponents. In general the minor components were eluted before the major component of the same molecular weight.

The major di- to penta-saccharide components were obtained in chromatographically pure form and their specific optical rotations and $R_M$ values were determined. Crystalline β-acetates were also prepared from the di-, tri-, and tetra-saccharides (see Table 1).

The disaccharide and its acetate had properties identical with those previously reported for laminaribiose.[11,12] When the $R_M$ values of the sugars or the molecular rotations of the sugars and their acetates were plotted against degree of polymerisation (known for the disaccharide and assumed for the higher oligosaccharides) linear relations were observed in all cases (see Figure). This behaviour characterises the tri- and higher saccharides as component members of the series of laminaridextrins. Further proof of the identity of

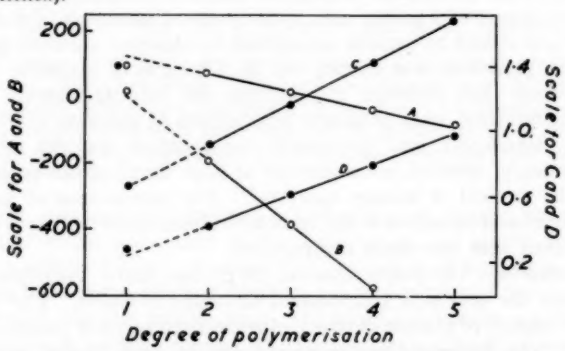
[12] Barry, *Sci. Proc. Roy. Dublin Soc.*, 1941, **24**, 423.
[13] Freudenberg and Oertzen, *Annalen*, 1951, **574**, 37.
[14] Barry, Dillon, and McGattrick, *J.*, 1942, 183.
[15] Barry, *J.*, 1942, 578.
[16] Peat, Thomas, and Whelan, *J.*, 1952, 722.
[17] Dillon and O'Colla, *Nature*, 1950, **166**, 67.
[18] Dillon and O'Colla, *Chem. and Ind.*, 1951, 111.
[19] Kylin, *Z. physiol. Chem.*, 1913, **83**, 171; 1915, **94**, 337.
[20] Gruzewska, *Bull. Soc. Chim. biol.*, 1923, **5**, 216.
[21] Friedlaender, Cook, and Martin, *Biochim. Biophys. Acta*, 1954, **14**, 136.
[22] Broatch and Greenwood, *Chem. and Ind.*, 1956, 1015.
[23] Peat, Whelan, and Lawley, *Biochem. J.*, 1953, **54**, xxxiii.
[24] Peat, Whelan, and Edwards, *J.*, 1955, 355.
[25] Peat, Whelan, Lawley, and Evans, *Biochem. J.*, 1955, **61**, x.

XUM

these substances came from paper-chromatographic examination of their partial acid hydrolysates. The trisaccharide gave rise to glucose and a single disaccharide (laminaribiose), the tetrasaccharide to a single di- and tri-saccharide and the pentasaccharide to a single tetrasaccharide, etc. In addition, laminaribiose was a product of the partial degradation of the trisaccharide by almond emulsin (β-glucosidase).

*Soluble Laminarin.*—A large-scale partial acid hydrolysate (27 g.) was prepared and fractionated as for insoluble laminarin. Only the mono-, di-, and tri-saccharide fractions were examined. It was again observed that each fraction contained more than one component and the amounts of the minor components were greater in proportion to the major components than for insoluble laminarin (see Part II). The properties of the major products (glucose, laminaribiose, and laminaritriose) are listed in Table 2. Products which had not been isolated from insoluble laminarin were L-fucose (0·39 g.), characterised as the phenylhydrazone, and traces of xylose and galactose. It is very probable that these arose by contamination of the soluble laminarin with fucoidin. A similar observation

*Physical properties of the laminaridextrins and their β-acetates. A, Molecular rotations (°) of free sugars; B, molecular rotations (°) of β-acetates; C, D, $R_M$ values of free sugars in solvents 1 and 2, respectively (see Experimental section).*




was previously made by Percival and Ross.[26] No oligosaccharides containing any of these three sugars were detected and it is not considered that they form part of the soluble laminarin molecule.

*Conclusions.*—These results prove that insoluble and soluble laminarin consist mainly of β-D-glucose residues joined continuously through 1 : 3-linkages and are entirely consistent with previous methylation studies.[8-10] The application of the technique of linkage analysis to the problem has, however, revealed previously unsuspected features of the structures of the two forms of the polysaccharide which merited further examination as described in the following paper.

## Experimental

*Analytical Methods.*—Paper chromatography was carried out on Whatman No. 1 or No. 54 paper; the irrigating solvents were (1) butan-1-ol–acetic acid–water (4 : 1 : 5, by vol.) or (2) butan-1-ol–pyridine–water (6 : 4 : 3, by vol.). Solutions of the sugars prepared from laminarin were treated before analysis with Somogyi's deproteinising reagents [27] (cf. ref. 28). Values of specific optical rotation of laminarin and the derived oligosaccharides are based on concentrations calculated from the glucose released on complete hydrolysis with acid,[29] together with rotations measured in a 4-dm. tube. All evaporations were made under diminished pressure at 40°, the aqueous solutions being kept at pH 5 by addition of sodium hydroxide or acetic acid.

[26] Percival and Ross, *J.*, 1950, 717.
[27] Somogyi, *J. Biol. Chem.*, 1945, **160**, 69.
[28] Whelan, Bailey, and Roberts, *J.*, 1953, 1293.
[29] Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224.

### *Insoluble Laminarin*

*Properties of the Polysaccharide.*—Insoluble laminarin was isolated from *L. cloustoni* as by Black *et al.*[7] and was kindly provided by Dr. E. T. Dewar. The dry material contained 92·5% of polyglucose [29] and 0·4% of non-volatile matter, and had $[\alpha]_D^{16}$ −13·4° (*c* 0·9 in water). The amorphous triacetate (52% yield; method of Percival and Ross [8]) had $[\alpha]_D^{16}$ −63·5° (*c* 0·4 in chloroform) [Found: Ac, 43·2. Calc. for $(C_{12}H_{16}O_8)_n$: Ac, 44·8%]. After complete hydrolysis (1·5N-sulphuric acid; 2 hr.; 100°) and neutralisation (barium carbonate), examination with benzidine spray [30] of the paper chromatograms (solvents 1 and 2) revealed glucose as the only reducing component, but silver nitrate–sodium hydroxide,[31] which detects reducing and non-reducing carbohydrates, revealed glucose and a substance of slightly greater $R_F$ value.

*Partial Acid Hydrolysis.—Isolation of the laminaridextrins.* In a preliminary experiment, laminarin (264 mg.) was hydrolysed in 0·33N-sulphuric acid (25 ml.) at 100° and portions were removed at intervals for determination of copper-reducing power.[32] After 2 hr. the apparent conversion into glucose was 39·0%, at which level a good yield of low-molecular-weight oligosaccharides was expected (cf. ref. 28). Accordingly, the large-scale hydrolyses were carried to this degree. Laminarin (11·04 g.) was dissolved in warm water (500 ml.) and diluted (to 1 l.) with 5N-sulphuric acid (66 ml.) and water. After 2 hr. at 100° the solution was poured on ice, brought to pH 8 with sodium hydroxide, and then made slightly acid (pH 5). The same procedure was repeated exactly and the hydrolysates combined. The apparent conversion into glucose was 33·8%. The solution was evaporated to dryness and a portion of the residue (50 mg.) was freed from electrolyte by extraction with pyridine.[33] Examination of the sugars by paper chromatography (solvent 1) revealed glucose and a series of reducing oligosaccharides. Less prominent were the non-reducing substance previously detected in the fully hydrolysed laminarin, and a series of non-reducing oligosaccharides. The remainder of the residue was dissolved in water (100 ml.) and much of the sodium sulphate removed by filtration. The filtrate and washings were adsorbed on charcoal–Celite (115 × 4 cm.) and the sugars eluted with water and stepwise-increasing concentrations of ethanol in water.[28] After suitable combination, the fractions were evaporated to dryness, the sugars dissolved in 80% methanol to eliminate inorganic matter, and the solutions re-evaporated. Paper-chromatographic fractionation (solvent 1) showed that the principal tri- and tetra-saccharide fractions were single substances. The main di- and penta-saccharide fractions were mixtures, however, and were refractionated by charcoal–Celite and paper (Whatman No. 3) chromatography, respectively. The monosaccharide fraction was mainly glucose, with a trace of the faster-moving non-reducing component. The yields of major products are shown in Table 1. In addition a non-reducing disaccharide (256 mg.), a non-reducing trisaccharide (*ca.* 100 mg.), gentiobiose (82 mg.), isomaltose (*ca.* 25 mg.), and several reducing trisaccharides other than laminaritriose (*ca.* 20 mg. of each) were isolated. Discussion of the significance of these minor components is reserved for the following paper.

*Acid and Enzymic Hydrolysis of the Major Tri-, Tetra-, and Penta-saccharides.*—A portion (*ca.* 20 mg.) of each sugar was hydrolysed in 0·33N-sulphuric acid (2 ml.) at 100° for 30 min., the solution neutralised with barium carbonate, and the supernatant liquid examined by paper chromatography in solvent 1. The trisaccharide yielded only laminaribiose and glucose; the tetrasaccharide gave laminaribiose and glucose and the trisaccharide, while the pentasaccharide gave rise to the tetra- and tri-saccharides, with laminaribiose and glucose. It seemed clear, therefore, that the tri-, tetra-, and penta-saccharides were laminari-triose, -tetraose, and -pentaose, respectively.

The trisaccharide (10 mg.) was incubated at 35° with a suspension of almond emulsion [34] (10 mg.) in water (1 ml.) for 1·5 hr. After the digest had been heated at 100° the supernatant solution was examined by paper chromatography (solvent 1). The substances located had $R_F$ values corresponding to the trisaccharide, laminaribiose, and glucose.

*Acetates of Glucose and the Laminaridextrins.*—Acetylation of the sugar (50—200 mg. quantities) was carried out with sodium acetate–acetic anhydride and the products were worked up in the usual way, being finally dissolved in ethanol, decolorised with charcoal, and allowed

[30] Bacon and Edelman, *Biochem. J.*, 1951, **48**, 114.
[31] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[32] Somogyi, *J. Biol. Chem.*, 1945, **160**, 61.
[33] Malpress and Morrison, *Nature*, 1949, **164**, 963.
[34] Tauber, *J. Biol. Chem.*, 1932—33, **99**, 257.

XUM

to crystallise. The yields varied from 74 to 90%. The pentasaccharide acetate failed to crystallise. The properties of the derivatives are listed in Table 1. Elementary analyses gave the following results. β-Laminaribiose octa-*O*-acetate (Found: C, 49·5; H, 5·7. Calc. for $C_{28}H_{38}O_{19}$: C, 49·6; H, 5·6%), *β-laminaritriose hendeca-O-acetate* (Found: C, 48·9; H, 5·8.

TABLE 1. *Properties of the main components of partly hydrolysed insoluble laminarin.*

| | Sugar | | | | β-Acetate | |
|---|---|---|---|---|---|---|
| | Yield [1] | $[\alpha]_D^{17-21}$ | $R_F$ value [2] | | | $[\alpha]_D^{17-21}$ |
| Substance | (g.) | in $H_2O$ | Solv. 1 | Solv. 2 | M. p. | in $CHCl_3$ |
| Glucose ..... | 3·62 | 52·7° | 0·18 | 0·35 | 132—133° | 3·8° |
| Laminaribiose ..... | 2·67 | 20·4 | 0·11 | 0·28 | 160—161 | −28·6 |
| Laminaritriose ..... | 2·02 | 2·4 | 0·065 | 0·20 | 120—121 | −40·0 |
| Laminaritetraose ..... | 1·6 | − 5·9 | 0·038 | 0·14 | 122—123 | −46·2 |
| Laminaripentaose ..... | 1·3 | −10·3 | 0·021 | 0·097 | — | — |

[1] From 22·08 g. of polysaccharide. The weights are those obtained in the first fractionation.
[2] Solvents are defined in the Experimental section.

$C_{40}H_{64}O_{27},H_2O$ requires C, 48·8; H, 5·7%), and *β-laminaritetraose tetradeca-O-acetate* (Found: C, 48·45; H, 5·8%. $C_{52}H_{70}O_{35},H_2O$ requires C, 49·1; H, 5·7%; $C_{52}H_{70}O_{35},2H_2O$ requires C, 48·4; H, 5·7%).

*Soluble Laminarin*

Soluble laminarin was isolated from *L. digitata* as by Black *et al.*[7] and was a gift from Dr. E. T. Dewar. The dried polysaccharide contained 91·2% of polyglucose [29] and 1·0% of non-volatile matter, and had $[\alpha]_D^{18}$ −11·9° (*c* 2·1 in water). The tri-*O*-acetyl derivative [8] had $[\alpha]_D^{17}$ −64·6° (*c* 0·9 in chloroform) [Found: Ac, 43·9. Calc. for $(C_{12}H_{16}O_8)_n$: Ac, 44·8%]. After complete acid hydrolysis, as for insoluble laminarin, paper chromatography revealed glucose with much smaller amounts of the same non-reducing component and fucose. The products of partial acid hydrolysis were the same as for insoluble laminarin, with fucose as an additional product.

*Large-scale Acid Hydrolysis.*—The rate of acid hydrolysis was the same as for insoluble laminarin. Accordingly, the polysaccharide (26·95 g.) was hydrolysed in 0·33N-sulphuric acid for 2 hr. at 100° and the hydrolysate (38·4% conversion) worked up and fractionated as previously described for insoluble laminarin, except that elution from the charcoal was discontinued after the emergence of the principal trisaccharide component.

The monosaccharide fraction contained glucose (see Table 2) with a much smaller amount of the non-reducing component, traces of xylose and galactose (identified by paper chromatography), and L-fucose (0·39 g.). The derived fucose phenylhydrazone had m. p. 166—167° (Found: C, 56·7; H, 7·5; N, 10·7. Calc. for $C_{12}H_{18}O_4N_2$: C, 56·7; H, 7·1; N, 11·0%). It was necessary to refractionate the disaccharide fraction on charcoal–Celite in order to obtain pure specimens of laminaribiose (Table 2), the non-reducing disaccharide, and gentiobiose. Isomaltose was not detected. As with insoluble laminarin the trisaccharide fraction consisted of a major component (laminaritriose) and minor components, *viz.*, a non-reducing trisaccharide and reducing trisaccharides. All these minor components are discussed in detail in the following paper.

TABLE 2. *Properties of the main components of partly hydrolysed soluble laminarin.*

| | Sugar [1] | | β-Acetate | |
|---|---|---|---|---|
| | Yield [2] | $[\alpha]_D^{14-19}$ | | $[\alpha]_D^{19-20}$ |
| | (g.) | in $H_2O$ | M. p. | in $CHCl_3$ |
| Glucose ..... | 5·82 | 50·9° | 132—133° | 3·8° |
| Laminaribiose ..... | 2·22 | 18·6 | 162—163 | −28·9 |
| Laminaritriose ..... | 2·41 | 2·0 | 120—121 | −40·1 |

[1] $R_F$ values were the same as in Table 1. [2] From 26·95 g. of polysaccharide. The weights of glucose and laminaritriose are those from the first fractionation, that of laminaribiose is after refractionation.

The glucose, and laminari-biose and -triose were identified by measurement of the physical properties of the sugars and their β-*O*-acetyl derivatives (Table 2).

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, September 18th,* 1957.

## 142. *The Structure of Laminarin. Part II.*[1] *The Minor Structural Features.*

By STANLEY PEAT, W. J. WHELAN, and H. G. LAWLEY.

Insoluble laminarin has been partly hydrolysed by acid, and the products fractionated. Fourteen mono-, di-, and tri-saccharide products have been identified and of these, D-glucose, D-mannitol, laminaribiose, gentiobiose, 1-*O*-β-glucosylmannitol, laminaritriose, 3-*O*-gentiobiosylglucose, 6-*O*-β-laminaribiosylglucose, and 1-*O*-β-laminaribiosylmannitol are considered to be true structural fragments of laminarin. It is suggested that the laminarin molecules may consist of unbranched chains of β-1 : 3-linked glucose units, occasionally interrupted by β-1 : 6-links, and that some, but not all, of the chains are terminated by mannitol. Soluble laminarin probably has a similar structure but contains a higher proportion of mannitol and of β-1 : 6-links. A method for the quantitative determination of mannitol in laminarin is described.

PREVIOUS work on the structure of laminarin has been summarised in the preceding paper,[1] in which confirmatory evidence was provided that the main polymeric linkage in this β-glucan is of the 1 : 3-type. Our investigations did not, however, confirm the view that laminarin is constituted solely of glucose residues or that the β-1 : 3-linkage is the only type present. We now report on additional structural features encountered in the two forms of laminarin, insoluble and soluble. Most of the work has been concerned with the insoluble form.

The conception of laminarin as a 1 : 3-linked β-glucan implies that a partial acid hydrolysate would contain one monosaccharide (glucose), one disaccharide (laminaribiose), and one trisaccharide (laminaritriose). We have actually isolated and characterised two monosaccharide components, three disaccharides, and four trisaccharides, in yields which seem to preclude the possibility that they are acid-reversion products. Laminarin cannot therefore be the simple polymer envisaged by earlier investigators.

The first indication of the complexity of the laminarin molecule came from an examination of the disaccharide fraction of the partial acid hydrolysate of insoluble laminarin (22·08 g.) in which were identified gentiobiose (82 mg.), isomaltose (25 mg.) and a non-reducing disaccharide (256 mg.) in addition to the laminaribiose (2·67 g.) previously reported.[1] The non-reducing substance was at first incorrectly identified as ββ-trehalose,[2] owing to a fortuitous coincidence of certain properties, in particular, specific optical rotation and $R_F$ value. The product was subsequently proved to be 1-*O*-β-D-glucopyranosyl-D-mannitol. A systematic study was therefore made of the components of an acid hydrolysate of a larger sample (137 g.) of insoluble laminarin.

*Mannitol and the Non-reducing Oligosaccharides.*—A search for mannitol in the monosaccharide fraction of the laminarin hydrolysate was first undertaken. The separation of glucose and mannitol by chemical means proved impracticable owing to the great excess of glucose and resort was had to the removal of the glucose by yeast fermentation. D-Mannitol (as the hexa-acetate) was obtained from the non-fermentable residue (see Table).

Crystalline mannitol hexabenzoate was later isolated from the acid hydrolysate of the non-reducing disaccharide mentioned above. The identity of this disaccharide with the 1-*O*-β-glucosylmannitol, previously found by Lindberg[3] in uncombined form in *Fucus vesiculosus*, was established as follows: (1) β-Glucosidase released glucose and mannitol.

[1] Part I, preceding paper.
[2] Peat, Whelan, and Lawley, *Biochem. J.*, 1953, **54**, xxxiii.
[3] Lindberg, *Acta Chem. Scand.*, 1953, **7**, 1119.



XUM

(2) The sugar (1 ml.) consumed 5·9 mol. of periodate and yielded 3·8 mol. of formic acid, the calculated values being 6 and 4 mol., respectively. (3) The disaccharide and an authentic sample of 1-*O*-β-glucosylmannitol had the same specific optical rotation, $R_F$ value, and $M_G$ value, and formed identical crystalline nona-*O*-benzoates (see Table).

In examining the "trisaccharide" fraction for non-reducing compounds, attention was concentrated on the four "trisaccharides" which could theoretically give rise to the "disaccharides" found in the hydrolysate, namely, laminaribiose, gentiobiose, isomaltose, and the glucosylmannitol. These non-reducing "trisaccharides" would include 1 : 6-di-*O*-β-glucosylmannitol. This would yield, on partial hydrolysis, 1- and 6-*O*-β-glucosylmannitols which, because of the central symmetry of mannitol, are alternative names for the same compound. Three of the four possible non-reducing substances were isolated from the "trisaccharide" fraction, namely, 1-*O*-β-laminaribiosylmannitol (1·1 g.), 1 : 6-di-*O*-β-glucosylmannitol (0·04 g.), and 1-*O*-β-isomaltosylmannitol (0·01 g.). The last two named components were not further examined because the yields in which they were obtained indicated that they might be artefacts produced by acid reversion. The laminaribiosylmannitol, however, was of obvious structural significance. It was identified on the following evidence: (1) Laminaribiose and 1-*O*-β-glucosylmannitol were the "disaccharide" products of its partial acid hydrolysis. (2) β-Glucosidase split off glucose to yield glycosylmannitol. (3) Mannitol isolated from a complete acid hydrolysate corresponded to 0·98 mole per mole of "trisaccharide." (4) The uptake of periodate (6·08 mol.) and the concomitant release of formic acid (3·72 mol.) and formaldehyde (1·03 mol.) were close to the calculated values of 6, 4, and 1 mol., respectively. (5) The specific optical rotation of the sugar and the properties of its crystalline acetate were identical with those of specimens obtained by chemical synthesis [4] (see Table).

*Reducing Components of the Laminarin Hydrolysate.*—The reducing monosaccharide components were D-glucose (55 g.) and L-fucose (0·55 g.) (see Table). It seems likely that the fucose arose from contamination of the laminarin with fucoidin. No fucose-containing oligosaccharides were found (cf. preceding paper [1]). The disaccharide components were laminaribiose (25 g.), gentiobiose (0·36 g.), and isomaltose (0·09 g.), all three being characterised as crystalline acetyl derivatives (see Table). There were four reducing trisaccharides, namely, laminaritriose (20 g.), 6-*O*-β-laminaribiosylglucose (0·36 g.), 3-*O*-β-gentiobiosylglucose (0·48 g.), and 3-*O*-β-isomaltosylglucose (0·12 g.). The last three substances were identified as follows:

6-O-β-*Laminarobiosylglucose.* (1) Partial acidic hydrolysis gave laminaribiose, gentiobiose, and glucose. (2) Exo-β-glucosidase gave gentiobiose and glucose. (3) The specific optical rotation of the sugar was close to the calculated value and to that of an authentic specimen prepared by chemical synthesis [5] and the crystalline acetyl derivatives of both specimens were identical (see Table).

3-O-β-*Gentiobiosylglucose.* (1) Partial acidic hydrolysis gave gentiobiose, laminaribiose, and glucose. (2) Exo-β-glucosidase liberated laminaribiose and glucose. (3) The specific optical rotation of the sugar was close to that of an authentic specimen [5] and to the calculated value (see Table).

3-O-β-*Isomaltosylglucose.* (1) Partial acid hydrolysis gave glucose, isomaltose, and laminaribiose. (2) Exo-β-glucosidase had no action on the sugar.

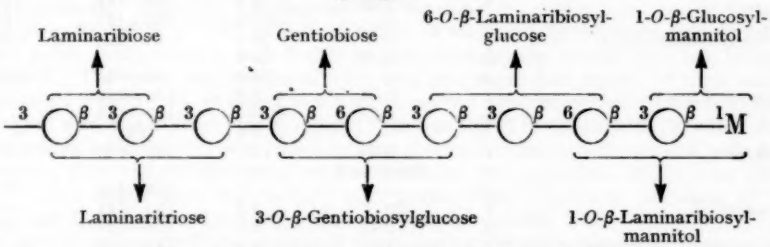
*The Structure of Insoluble Laminarin.*—The foregoing account has shown that fourteen mono-, di-, and tri-saccharide components of the partial acid hydrolysate of laminarin were identified. The question arises whether any of these are artefacts derived from contaminants of the polysaccharide or formed by acid-reversion reactions. There is no doubt as to the origin of the glucose and laminari-biose and -triose, but the fucose is not considered to have any structural significance (see above). The source of the mannitol and the related non-reducing oligosaccharides requires more detailed consideration. It

[4] Peat, Whelan, Lawley, and Evans, *Biochem. J.*, 1955, **61**, x.
[5] Peat, Whelan, and Evans, to be published.

XUM

will be recalled that Lindberg [3] found mannitol, 1-*O*-β-glucosylmannitol, and 1 : 6-di-*O*-β-glucosylmannitol in the uncombined state in an extract of *Fucus vesiculosus* but chromatographic examination of the unhydrolysed laminarin failed to reveal the presence of these sugars. If mannitol is an integral part of the laminarin molecule then the partial hydrolysate should contain an oligosaccharide in which both mannitol and 1 : 3-linked β-glucose residues are present. Such a substance was found, namely, 1-*O*-β-laminaribiosylmannitol. In a preliminary communication we reported that this sample of insoluble laminarin contained 1 mole of mannitol to 58 moles of glucose.[6] (The method of estimating the mannitol content of laminarin is described below.) The mannitol present in the 1-*O*-β-glucosylmannitol and the 1-*O*-β-laminaribiosylmannitol represented about 50% and 15%, respectively, of the total mannitol in the amount of laminarin (137 g.) submitted to partial hydrolysis. It is concluded that the reducing ends of at least some of the glucose chains of laminarin are combined glycosidically with the primary hydroxyl groups of D-mannitol. The possibility exists that some of the mannitol residues are incorporated within the polysaccharide chains rather than as terminal units. In such a case, however, it is to be expected that oligosaccharides would be liberated, by partial hydrolysis, in which a mannitol unit is flanked by glucose units. One such fragment, namely, 1 : 6-di-*O*-β-glucosylmannitol, was in fact isolated, but in an amount so small relative to the yield of laminaribiosylmannitol (see Table) that it would be unwise to

*Suggested structure of laminarin, showing the origin of the di- and tri-saccharides produced by partial hydrolysis.*




Key: ○ = D-glucopyranose unit; M = mannitol
(N.B. Some of the molecules do not contain mannitol.)

ascribe a structural significance to it until more is known about the participation of mannitol in acid-reversion reactions. All that can be said at this stage is that a very large majority of the mannitol residues in laminarin are terminal units.[4] It has been shown that when glucose is heated in acid under the same conditions as for the hydrolysis of insoluble laminarin (0·33N-sulphuric acid for 3 hr. at 100°) about 0·04% is converted into gentiobiose and 0·06% into isomaltose.[7] The yields of these two sugars from insoluble laminarin were 0·26% and 0·06%, respectively, suggesting that while the β-1 : 6-link may be present in laminarin, the α-1 : 6-link is not. Support for the presence of a small proportion of β-1 : 6-links comes from the isolation of significant amounts of 3-β-gentiobiosylglucose and 6-β-laminaribiosylglucose.

The Figure shows diagrammatically a section of a laminarin chain which on partial hydrolysis would yield those of the oligosaccharides isolated which are considered to be true structural entities. This makes laminarin a linear molecules terminated by mannitol and containing mainly β-1 : 3-linked glucose units, interrupted by an occasional β-1 : 6-linkage. We have as yet no information on the possible branching of the molecule. The 1 : 6-bonds could represent points of branching but if this were so, a partial hydrolysate

[6] Peat, Whelan, and Lawley, *Chem. and Ind.*, 1955, 35.
[7] Peat, Whelan, Edwards, and Owen, *J.*, 1958, 586.

XUM

might be expected to contain 3 : 6-di-*O*-β-glucosylglucose. We were unable to detect this sugar in the laminarin hydrolysate but such negative evidence cannot be regarded as conclusive.

This representation of laminarin is not intended to imply that all molecules are terminated by mannitol. On the contrary, we have evidence, which will be published later, that samples of insoluble laminarin contain roughly equal numbers of reducing and non-reducing molecules. This is in agreement with a recent report by Unrau and Smith.[8]

The fact that some of the laminarin chains are terminated by mannitol means that they will be completely protected from the erosive actions of both alkali and periodate. Each of these reagents degrades unprotected β-1 : 3-linked glucose polymers stepwise

*Physical properties of the partial hydrolysis products of insoluble and soluble laminarin.*

| Sugar [a] | Source [b] | Yield [c] (g.) | $[\alpha]_D$ in $H_2O$ | β-Acetate m. p.[d] | β-Acetate $[\alpha]_D$ in $CHCl_3$ |
|---|---|---|---|---|---|
| D-Glucose | I | 55 | +51·1° | 132—133° | — |
| | S | 5·82 | +50·9 | 132—133 | + 3·8° |
| | A | — | +52·6 | 135·5 | + 3·8 |
| D-Mannitol | I | 0·55 | — | 122—123 | +25·0 |
| | A | — | — | 122 | +25·0 |
| L-Fucose | I | 0·55 | — | 169 | L-Fucose phenylhydrazone |
| | S | 0·39 | — | 166—167 | |
| | A | — | — | 170—173 | |
| Laminaribiose | I | 25 | +19·1 | 162 | −28·2 |
| | S | 2·22 | +18·6 | 162—163 | −28·9 |
| | A | — | +18·6 | 160—161 | −28·8 |
| 1-*O*-β-Glucosylmannitol | I | 2·3 | −20·7 | 88—92 | +39·7 [e] |
| | S | 0·37 | −20·4 | — | — |
| | A | — | −20·0 | 88—94 | +39·7 [e] |
| Gentiobiose | I | 0·36 | + 8·5 | 191—192 | − 4·8 |
| | S | 0·31 | + 9·4 | 192—193 | − 5·0 |
| | A | — | + 9·6 | 193 | − 5·3 |
| Isomaltose | I | 0·09 | +121 | 145—146 | +97·5 |
| | S | Not found | — | — | — |
| | A | — | — | 143—144 | +97 |
| Laminaritriose | I | 20 | + 2·3 | 120—121 | −40·4 |
| | S | 2·41 | + 2·0 | 120—121 | −40·1 |
| 1-*O*-β-Laminaribiosylmannitol | I | 1·1 | −24·8 | 144—145 | −18·6 |
| | A | — | −24·3 | 144—145 | −17·9 |
| | C | — | −24·3 | — | — |
| 3-*O*-β-Gentiobiosylglucose | I | 0·48 | − 1·0 | — | — |
| | A | — | − 2·1 | — | — |
| | C | — | − 3·2 | — | — |
| 6-*O*-β-Laminaribiosylglucose | I | 0·36 | − 4 | 214—215 | −27 |
| | A | — | − 6·0 | 216—217 | −27·4 |
| | C | — | − 3·5 | — | −24·2 |

[a] Also isolated from insoluble laminarin were 3-*O*-β-isomaltosylglucose (0·12 g.; $[\alpha]_D^{18°}$ +67° in water), 1 : 6-di-*O*-β-glucosylmannitol (0·04 g.; $[\alpha]_D^{18°}$ −16·5° in water), 1-*O*-β-isomaltosylmannitol (0·01 g.), an isomaltose-containing tetrasaccharide (0·11 g.), and two unidentified sugars (*A* and *B*, see Experimental section). [b] I = Insoluble laminarin, S = soluble laminarin, A = authentic specimen, C = calculated value (see Experimental section). [c] From 180 g. of undried insoluble laminarin containing 137 g. of polyglucose hydrolysed to 55% conversion into glucose and from 26·95 g. of dried soluble laminarin containing 24·6 g. of polyglucose. [d] Mixed m. p. determinations with authentic specimens were carried out wherever possible. No depression was observed. [e] Benzoyl derivative.

from the reducing chain ends. A 1 : 6-linkage in such a chain presents a barrier to erosion, reaction ceasing when the 1 : 6-link is reached by the reagent. It is found in practice that only about half of the glucose residues of insoluble laminarin are eliminated by alkali [8] or periodate [9] and these results have been explained by postulating the existence of 1 : 6-links in the molecule. This interpretation has in turn been used in support of the

[8] Unrau and Smith, *Chem. and Ind.*, 1957, 330.
[9] Corbett and Kenner, *J.*, 1955, 1431.

idea of branching,[10] despite the published evidence[2,4,6] that two types of "blocking" structure are present in laminarin. It is clear that the presence of mannitol units in the laminarin molecule invalidates any conclusions from the alkali or periodate experiments concerning the presence of 1 : 6-links.

*The Structure of Soluble Laminarin.*—Soluble laminarin has been examined in less detail than the insoluble form. The results were much the same as for insoluble laminarin except that the minor structural features, in the form of mannitol and β-1 : 6-links, were more prominent (see Table). The minor trisaccharides were not examined so that the question of branching remains unresolved.

## Experimental

*Analytical and General Methods.*—Most of the methods are described in the preceding paper [1] and by Peat, Whelan, and Roberts.[12] When $[\alpha]_D$ values of free sugars and laminarin were being measured, the concentrations were determined by acidic hydrolysis to glucose;[13] the concentrations of ester derivatives were measured by weighing. Optical rotations were measured in 4-dm. tubes. M. p.s are uncorrected.

Most paper-chromatographic observations and all preparative paper chromatography was carried out with butan-1-ol–acetic acid–water (4 : 1 : 5, by vol.) as the irrigating solvent. To effect a clear-cut separation of glucose and mannitol the solvents used were ethyl acetate–acetic acid–water (3 : 1 : 1, by vol.) and phenol–water (4 : 1, by weight).

Periodate oxidations were carried out by mixing equal volumes of 0·37M-sodium metaperiodate and sugar solution (0·3—1·4 mg./ml.), and then storing the mixture in the dark at room temperature. Periodate consumption was measured by adding 1 ml. of the digest to a mixture of water (50 ml.), 10% potassium iodide (3 ml.), and 2N-sulphuric acid (2 ml.), the liberated iodine being titrated with 0·033N-sodium thiosulphate, starch glycollate being used as indicator. The titre was compared with that of a sugar-free digest. Formic acid was determined by adding 1 ml. of digest to 0·3 ml. of neutral ethylene glycol. After the sides had been washed with water (5 ml.) the stoppered flask was stored in the dark for 30 min. Neutral 10% potassium iodide (2 ml.) was added and the liberated iodine rapidly titrated with 0·005N-thiosulphate, starch glycollate being used as indicator. A sugar-free digest was similarly titrated. This blank titre was usually nil. Under these conditions oxidation of 1-*O*-β-glucosyl- and 1-*O*-β-laminaribiosyl-mannitol was complete within 2 hr.

The specific optical rotations of some of the trisaccharides were calculated by regarding the sugar as a disaccharide substituted in its non-reducing glucose unit by β-glucose in 1 : 3- or 1 : 6-combination. For example, the molecular rotation and hence $[\alpha]_D$ of 1-*O*-β-laminaribiosyl-mannitol was calculated by adding together the molecular rotation of 1-*O*-β-glucosylmannitol and the molecular rotational increment in the series of laminaridextrins, taken from the results given in Part I.[1] The other molecular rotational increment required was that of the gentiodextrin series of sugars and was taken from the values given by Haq and Whelan.[14]

### *Insoluble Laminarin*

*Partial Hydrolysis of Insoluble Laminarin.*—Insoluble laminarin, isolated from *Laminaria cloustoni* as by Black, Cornhill, Dewar, and Woodward,[15] was kindly provided by Dr. E. T. Dewar. The vacuum-dried polysaccharide contained 93·1% of polyglucose, and 0·33% of non-volatile matter, and had $[\alpha]_D^{16}$ −10·9° (*c* 0·8 in water). The amorphous triacetate (56% yield, method of Percival and Ross [16]) had $[\alpha]_D^{15}$ −65·6° (*c* 0·45 in chloroform) [Found: Ac, 43·5. Calc. for $(C_{12}H_{16}O_8)_n$: Ac, 44·8%]. Paper-chromatographic analysis of a sample hydrolysed to completion with sulphuric acid [1] showed the presence of a major component with the $R_F$ value of glucose and small amounts of substances corresponding to mannitol and fucose.

[10] Hough and Perry, *Chem. and Ind.*, 1956, 768.
[11] Broatch and Greenwood, *Chem. and Ind.*, 1956, 1015.
[12] Peat, Whelan, and Roberts, *J.*, 1957, 3916.
[13] Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224.
[14] Haq and Whelan, *J.*, 1956, 4543.
[15] Black, Cornhill, Dewar, and Woodward, *J. Appl. Chem.*, 1951, **1**, 505.
[16] Whelan, Bailey, and Roberts, *J.*, 1953, 1293.

XUM

Two batches of the laminarin were hydrolysed as described previously.[1] Each contained 68·5 g. of polyglucose. The times of hydrolysis at 100° were 165 min. and 170 min., when the percentage apparent conversions into glucose, measured on the neutralised hydrolysates, were 53·4% and 55·3%, respectively. The combined solutions were concentrated to about 1 l., crystallised sodium sulphate being removed from time to time. Paper chromatography showed that glucose, mannitol, fucose, laminaridextrins, and non-reducing oligosaccharides were present. The concentrate was adsorbed on charcoal–Celite (120 × 8·1 cm.; equal weights of B.D.H. "activated charcoal" and Celite no. 535) and the monosaccharide fraction eluted under suction with water. Oligosaccharides were then desorbed by feeding the column from a reservoir initially containing 20 l. of water, the level in which was automatically maintained by a feed of 20% ethanol. After 195 fractions (500 ml. each) had been collected the column was eluted with 50% ethanol until the optical rotation had returned to zero and then with 25% propan-1-ol. The last two fractions weighed 22·5 g. and 24·9 g., respectively, and contained laminaritriose and sugars of higher molecular weight. Fractions 1—195 were examined for optical rotation and the separated sugars were obtained dry as already described.[1, 12, 16]

*Monosaccharides.*—(a) *Glucose.* Fractions 1—42 (58·5 g.) contained glucose and mannitol. The glucose content was measured by reducing power and the sugar identified by measurement of $[\alpha]_D$ and formation of the crystalline acetyl derivative (89% yield, see Table).

(b) *Mannitol.* To isolate the mannitol it was necessary to remove the large excess of glucose. Attempted removal (in control experiments) of glucose as glucosazone or lead gluconate was unsuccessful and the glucose was therefore converted into the mixed methyl α- and β-glucosides and the charcoal-chromatographic separation of mannitol from the glucosides examined. The desired separation was not however achieved and the glucose was recovered by hydrolysis. Fermentation with yeast was next attempted, control experiments (see later) having shown that the yeast did not introduce any substance which might be mistaken for mannitol.

The mixture (32 g.) was dissolved in water (600 ml.) and treated with fresh baker's yeast (33 g.) for 36 hr. at 30°. After being passed through a Seitz filter, the solution was shown by paper-chromatographic examination to contain mannitol, levoglucosan, isomaltose and/or gentiobiose. These products, apart from the mannitol, were probably formed from glucose during the acidic hydrolysis of the methyl glucosides. They were removed by hydrolysing the solid residue (5·6 g.) in 1·5N-sulphuric acid (2 l.) at 100° for 2 hr. After neutralisation with barium carbonate, the dried residue was extracted with 80% aqueous methanol, the solution evaporated to dryness, and the residue dissolved in water (200 ml.) and again fermented with yeast (10 g.). Only traces of sugars then remained. The syrupy residue (3·7 g.) was acetylated with sodium acetate–acetic anhydride and crystalline D-mannitol hexa-*O*-acetate (1·3 g.) was obtained. This corresponds to 0·55 g. of free mannitol.

(c) *Fucose.* Fractions 43—54 (0·55 g.) contained fucose and a trace of glucose. The The fucose was identified as the phenylhydrazone [17] (51% yield).

*Disaccharides.*—The sugars are mentioned in order of their elution from the charcoal column.

Fractions 55—61 (0·53 g.) contained isomaltose and the non-reducing disaccharide (1-*O*-β-glucosylmannitol). Fractions 62—68 (2·87 g.) contained the glucosylmannitol, gentiobiose, and traces of laminaribiose and glucose. The two batches were combined and refractionated on charcoal–Celite (57 × 4 cm.) which was eluted with water (2 l.), 4% ethanol (5·6 l.), and then 5% ethanol (2·5 l.), 100 ml. fractions being collected. Products were thereby obtained consisting of isomaltose (0·12 g.) with trace of glucosylmannitol, pure glucosylmannitol (1·37 g.), and fractions containing increasing amounts of gentiobiose mixed with glucosylmannitol (1·1 g.).

(a) *Isomaltose.* The isomaltose fraction was acetylated with sodium acetate—acetic anhydride but the product (179 mg.) did not crystallise. It was fractionated on charcoal–Celite [18] and a crystalline fraction (64 mg.) was obtained having the properties of β-isomaltose octa-acetate. A portion of this acetate was deacetylated [19] in order to measure the $[\alpha]_D$ of the free sugar (see Table).

(b) 1-O-β-D-*Glucopyranosyl*-D-*mannitol.* The chromatographically pure sugar (295 mg.)

[17] Black, Cornhill, Dewar, and Woodward, *J. Sci. Food Agric.*, 1953, **4**, 85.
[18] Morgan and Whelan, to be published.
[19] Bates, "Polarimetry, Saccharimetry, and the Sugars," U.S. Government Printing Office, Washington, 1942, p. 493.

was hydrolysed in 1·5N-sulphuric acid (50 ml.) at 100° until the optical rotation was constant (3 hr.). After neutralisation (barium carbonate) and evaporation the residue (271 mg.) was boiled with 0·25% (w/v) methanolic hydrogen chloride for 90 hr. and then neutralised with silver carbonate. The residue (204 mg.) contained methyl glucoside, mannitol, and a trace of unchanged disaccharide and was fractionated on thick filter paper [12] to yield crystals of methyl α-D-glucoside (53 mg.), m. p. and mixed m. p. 165—166°, $[\alpha]_D^{17}$ +158° (in water). The mannitol residue (76 mg.) was benzoylated [20] to yield crystals (103 mg.) which on recrystallisation from acetone–ethanol gave the hexa-*O*-benzoate, m. p. and mixed m. p. 150—151°, $[\alpha]_D^{16}$ +52·4° (in chloroform). Mannitol and glucose were also identified chromatographically after the disaccharide had been treated with hot 1·5N-sulphuric acid or with almond β-glucosidase.[1]

The disaccharide (137 mg.) was benzoylated [20] and the resulting syrup (605 mg.) deposited crystals (175 mg.) from ethanol which after two further recrystallisations gave 1-*O*-β-D-gluco-pyranosyl-D-mannitol nona-benzoate. A second specimen was prepared for comparison from an authentic sample of the disaccharide kindly supplied by Dr. Bengt Lindberg, The mixed m. p. showed no depression. All attempts by ourselves and by Dr. Lindberg to obtain a crystalline acetyl derivative have failed.

(c) *Gentiobiose.* Gentiobiose was contained in fractions 55—68 (see above). Fractions 69—75 (9·08 g.) contained mainly laminaribiose with small amounts of glucosylmannitol and gentiobiose. The amounts of gentiobiose in these fractions were estimated by quantitative chromatography on thick filter paper. Because of the similarity of $R_P$ value, quantitative separation of gentiobiose from glucosylmannitol was not attempted. The gentiobiose content of the mixture of the two sugars was estimated by measuring the reducing power with Somogyi reagent [21] which had been calibrated against authentic gentiobiose. For identification some of the gentiobiose in Fractions 69—75 was separated by prolonged irrigation on thick filter paper. The $[\alpha]_D$ of the sugar was measured and its crystalline acetate prepared (65% yield).

(d) *Laminaribiose.* Fractions 76—95 (17·73 g.) contained only laminaribiose. A new derivative of laminaribiose was prepared by treating laminaribiose solution (2·08 g.; 20 ml.) with potassium borohydride solution (526 mg.; 10 ml.) at 20°. The rotation became constant after 3 hr. and 6N-acetic acid was then added until the pH was 4·5. The residue (4·34 g.) obtained by neutralisation with sodium hydroxide and evaporation was treated with sodium acetate–acetic anhydride. The product was *laminaribi-itol nona-acetate*, m. p. 108—109° (from ethanol), $[\alpha]_D^{18}$ −10·8° (*c* 0·53 in chloroform) (Found: C, 49·5; H, 6·1. $C_{30}H_{42}O_{20}$ requires C, 49·9; H, 5·8%).

*Trisaccharides.*—(a) *Sugars present in trace amounts.* Fractions 96—139 segregated in five batches contained laminaribiose, laminaritriose, and five other sugars. These batches were separately fractionated by chromatography on thick filter paper and examined by partial hydrolysis with sulphuric acid and with emulsin,[1, 12] Three of the components were identified as 3-*O*-β-isomaltosylglucose {movement in butan-1-ol–acetic acid–water relative to laminaribiose ($R_L$ = 0·52), $[\alpha]_D^{18}$ +67° (in water)}, 1-*O*-β-isomaltosylmannitol ($R_L$ = 0·44), and 1 : 6-di-*O*-β-glucosylmannitol {$R_L$ = 0·3; $[\alpha]_D^{18}$ −16·5 (in $H_2O$); literature [3] $[\alpha]_D^{20}$ −14°}, possibly containing some 1-*O*-β-gentiobiosylmannitol. The other two components (*A*, *B*) which were not identified, gave glucose, laminari-biose and -triose, and higher saccharides on partial acid hydrolysis. Sugar *A* (65 mg.) had $R_L$ = 0·24, $[\alpha]_D^{18}$ +10·7° (*c* 0·07 in water). Sugar *B* (59 mg.) had $[\alpha]_D^{18}$ −6·9° (*c* 0·09 in water).

(b) 1-O-β-*Laminaribiosylmannitol.* Fractions 140—148 (1·01 g.) consisted mainly of a non-reducing trisaccharide with traces of laminari-biose and -triose. The whole fraction was purified by chromatography on thick filter paper to yield 601 mg. of pure sugar ($R_L$ = 0·44). Reference is made above to the products of its partial acidic and enzymic hydrolysis. The mannitol content of the trisaccharide corresponded to 0·98 mol. The specific optical rotation of the sugar and the properties of its crystalline acetyl derivative (75% yield) are shown in the Table. Measurements were made of the consumption of periodate and the formation of formic acid and of formaldehyde. The sugar solution (6 ml.; 49·4 mg.) was treated with the amount of 1% sodium metaperiodate required for complete oxidation (12·55 ml., 6 mol.) and then stored in the dark for 64 hr. at room temperature; 0·2% aqueous dimedone solution (50 ml.) was then added. After being kept overnight the formaldehyde derivative was filtered off (29·3 mg., 1·03 mol.; m. p. 184—185°, literature, m. p. 188°).

[20] Wolfrom and Gardner, *J. Amer. Chem. Soc.*, 1943, **65**, 750.
[21] Somogyi, *J. Biol. Chem.*, 1945, **160**, 61.

XUM

(c) 6-O-β-*Laminaribiosylglucose*. Fractions 149—161 (1·62 g.) contained approximately equal amounts of laminaribiosylmannitol ($R_L = 0·46$), laminaritriose ($R_L = 0·65$), and a reducing sugar ($R_L = 0·40$) migrating between laminari-triose and -tetraose. Laminaritriose was removed by chromatography on thick filter paper but the others were too close in $R_F$ value for clear-cut separation. A successful separation was achieved by converting the reducing sugar (Barker, Bourne, and O'Mant's method [22]) into its methyl furanoside, this having $R_L = 1·0$. The mixture (699 mg.) was dissolved in 4% (w/w) methanolic hydrogen chloride (35 ml.) by shaking it for 20 min. and set aside at room temperature. The optical rotation became constant (−0·01°; 0·5-dm. tube) after 135 min. and freshly prepared dry silver carbonate (5 g.) was then added. The neutral solution was filtered, the silver residue washed with methanol (3 × 20 ml.), and the combined filtrates evaporated over barium carbonate (freshly washed and dried). Paper chromatography showed the mixture (600 mg.) to be free from reducing sugar and it was fractionated on thick filter paper to yield laminaribiosylmannitol (302 mg.) and the methyl furanoside (104 mg.). The laminaribiosylmannitol was identified by partial acidic and enzymic hydrolysis. The methyl furanoside was hydrolysed in 0·01N-hydrochloric acid (100 ml.) at 44—46°, the reaction being followed by measurement of reducing power, which was constant after 120 hr. After neutralisation (silver carbonate) and isolation in the usual way, the product (48 mg.) contained reducing sugar ($R_L = 0·40$) and some unchanged glycoside. The reducing sugar was separated on thick filter paper and the product (23 mg.) examined by partial acidic and enzymic hydrolysis (see above). The specific optical rotation was measured and the crystalline acetate prepared.

(d) *Laminaritriose*. Fractions 162—171 (4·33 g.) contained laminaritriose and 6-*O*-β-laminaribiosylglucose. The amount of the latter was estimated by quantitative separation on thick filter paper and hydrolysis to glucose.[13] Fractions 172—195 (9·47 g.) contained only laminaritriose which was characterised as shown in the Table.

(e) 3-O-β-*Gentiobiosylglucose*. The dextrins eluted from the charcoal column by 50% ethanol and 25% propan-1-ol (see above) were refractionated on charcoal–Celite (1 : 1; 145 × 6 cm.) by elution with 22·5% ethanol (9 l.) and then 25% ethanol (4 l.). The first 4 l. of eluate contained no sugar. Subsequently the eluate was collected in 1 l. fractions which were examined by paper chromatography, with the following results: (*a*) glucose and laminari-biose and -triose (0·40 g.), (*b*) laminaritriose (3·89 g.), (*c*) laminaritriose (1·96 g.), (*d*) equal amounts of laminaritriose and a reducing sugar, *X*, migrating between laminari-triose and -tetraose (0·91 g.), (*e*) as (*d*) (0·41 g.), (*f*) as (*d*) with a reducing sugar, *Y*, moving between laminari-triose and -tetraose (0·30 g.), (*g*) laminaritriose, *Y*, and a non-reducing tetrasaccharide (0·61 g.), (*h*) equal amounts of laminaritetraose and non-reducing tetrasaccharide with a trace of *Y* (0·92 g.), (*i*) and (*j*) laminaritetraose (4·00 g.). Fractions (*e*) and (*f*) were further fractionated on thick filter paper to yield *X* (183 mg.), *Y* (106 mg.), and laminaritriose (154 mg.). On partial acidic hydrolysis, *X* gave laminaribiose, gentiobiose, and glucose; *Y* gave glucose, laminaribiose, isomaltose, laminaritriose, and a trisaccharide with the $R_F$ value of 3-*O*-isomaltosylglucose; and laminaritriose gave laminaribiose and glucose. When treated with emulsin, *X* gave laminaribiose and glucose, *Y* was not attacked, and laminaritriose gave laminaribiose and glucose. It was concluded that *X* was 3-*O*-β-gentiobiosylglucose and *Y* was the tetrasaccharide *O*-α-D-glucopyranosyl-(1 ⟶ 6)-*O*-β-D-glucopyranosyl-(1 ⟶ 3)-*O*-β-D-glucopyranosyl-(1 ⟶ 3)-D-glucose. The yield of *X*, characterised by its specific optical rotation, was determined by adding the weight already obtained (183 mg.) to that estimated to be in fraction (*d*) by quantitative chromatography (295 mg.).

### *Soluble Laminarin*

The properties of the sample of soluble laminarin and the details of its hydrolysis and fractionation are described in the preceding paper.[1] Glucose and fucose were isolated and characterised; mannitol was detected by paper chromatography. Glucosylmannitol, gentiobiose, laminaribiose, and laminaritriose were also characterised (see Table).

### *Estimation of Mannitol in Laminarin.*

To estimate mannitol advantage was taken of the large specific optical rotation which mannitol exhibits in the presence of acid ammonium paramolybdate ($[\alpha]_{5461}^{20}$ + 169°; ref. 23).

[22] Barker, Bourne, and O'Mant, *Chem. and Ind.*, 1955, 425.
[23] Frèrejacque, *Compt. rend.*, 1935, **200**, 1410; 1939, **208**. 1123.

XUM

In the absence of molybdate, $[\alpha]_D$ is only $-0{\cdot}24°$. The intention was to hydrolyse laminarin with acid, to remove glucose by fermentation with baker's yeast, and then to measure the optical rotation. The stages in the development of the method were as follows:

(i) It was shown that a direct proportionality existed between $\alpha_D$ and concentration of D-mannitol in the range 0—0·19% mannitol in the presence of 1% ammonium paramolybdate and 0·1N-sulphuric acid. The measured $[\alpha]_D^{17}$ of mannitol–molybdate was $+139{\cdot}3°$.

(ii) Glucose (10 g.) in water (200 ml.) was incubated with baker's yeast (11 g.) for 19 hr. at 30° in the presence and absence of mannitol (1 g.). The digests were passed through a Seitz filter and examined by paper chromatography. Glucose, but not mannitol, had completely disappeared and the solutions had no detectable optical activity.

(iii) Mannitol (1 g.) was incubated with a suspension of yeast (10 g.) in water (200 ml.) at 30°. At intervals filtered portions (5 ml.) were diluted to 25 ml. with water only or with, in addition, 5% molybdate (5 ml.) and 5N-sulphuric acid (0·5 ml.) to give the 1% final concentration of molybdate and 0·1N concentration of acid used in all experiments. A yeast suspension free from mannitol was treated in the same way. Only the mannitol–molybdate solution showed optical activity. This was constant during the period 0—48 hr. but fell progessively thereafter, being 93·9%, 80·4%, and 54·7% of its initial value after 71, 95, and 119 hr. In subsequent experiments, therefore, the yeast treatment was continued for not more than 36 hr.

(iv) Four digests containing mannitol (24—240 mg.), glucose (2 g.), yeast (2 g.), and water to 43 ml. were incubated at 30° for 36 hr. in 50 ml. graduated cylinders plugged with cotton wool. After addition of water to 43 ml. to adjust for slight evaporation, the digests were filtered and 5—10 ml. portions diluted to 25 ml. with molybdate and acid or with water. The molybdate solutions were optically active and the recoveries of mannitol corresponded to 104·2% (from 24 mg. of mannitol), 100·9% (72 mg.), 99·5% (120 mg.), 100·7% (240 mg.).

(a) *Insoluble Laminarin.*—The sample examined was that described earlier in this paper. Two vacuum-dried samples (*A*, 1·9476 g.; *B*, 1·9783 g.) were each dissolved in water (200 ml.), and 36N-sulphuric acid (21·5 ml.) and water to 500 ml. were added. After being heated at 100° for 3 hr. the cooled solutions were neutralised with barium carbonate (90 g.) overnight and the filtrate and water washings evaporated to dryness. Aqueous solutions of the residues were filtered, made up to 100 ml. with washings, and incubated with baker's yeast (2 g.) for 36 hr. at 30°. The yeast was removed on a Seitz filter and washed, the filtrates evaporated, and the residues each fractionated on thick filter paper to remove unfermentable reversion products and fucose. The mannitol was extracted with water (3 × 500 ml.) and the extracts evaporated to 20 ml., filtered, and diluted to 50 ml. One portion (15 ml.) was diluted to 25 ml. with water and two further 15-ml. portions with 5% molybdate and 5N-sulphuric acid such that the final concentrations of these reagents were in one case 1% and 0·1N and in the other 1·6% and 0·2N respectively. The water solutions were optically inactive; the molybdate solutions had $\alpha_D$ $+0{\cdot}216°$, $+0{\cdot}213°$ (Sample *A*), and $+0{\cdot}213°$, $+0{\cdot}217°$ (Sample *B*), respectively. These values, taken with the measured polyglucose content (93·1%, see above), correspond to molar ratios of glucose : mannitol of 57·5 : 1 and 58·4 : 1, respectively.

(b) *Soluble laminarin.* Samples of the specimen of soluble laminarin described in Part I [1] (1·8453 g. and 1·8418 g.) were treated as for insoluble laminarin. The glucose : mannitol ratios found were 37·1 : 1 and 37·9 : 1, respectively.

We thank Dr. E. T. Dewar for the gift of the laminarin samples referred to in Parts I and II and the Department of Scientific and Industrial Research for the award of a maintenance grant (to H. G. L.).

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, September 18th*, 1957.]

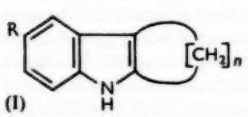
XUM

## 143. *Carcinogenic Nitrogen Compounds. Part XXIV.* The Synthesis of Indole and Quinoline Compounds from Cyclic Ketones.*

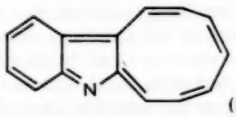
By Ng. Ph. Buu-Hoï, P. Jacquignon, and T. B. Loc.

Indole, benzindole, and quinoline compounds fused to an 8-, 9-, or 10-membered *cyclo*alkene ring have been synthesised by the Fischer and the Pfitzinger reaction from *cyclo*octanone, *cyclo*nonanone, and *cyclo*decanone; the compounds are not dehydrogenated by chloranil. Fischer cyclisation of phenylhydrazones of α-substituted *cyclo*hexanones to carbazolenines is discussed, and the properties of some of these bases are reported.

Treibs, Steinert, and Kirchhof [1] recently reported the dehydrogenation of 2 : 3-*cyclo*heptenoindole to 1-aza-2 : 3-benzazulene by means of chloranil; the possibility therefore exists, at least in theory, of preparing the next higher, fully conjugated analogous heterocycle (II), by dehydrogenation of 2 : 3-*cyclo*nonenoindole (I; R = H, $n = 7$). Since highly conjugated molecules such as (II) would be of interest as potential carcinogens, an attempt was made to prepare them in this way. 2 : 3-*cyclo*Nonenoindole and its 5-methyl



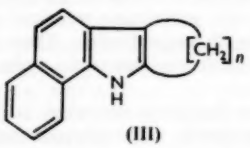

(I)



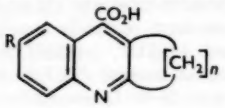

(II)

homologue (I; R = Me, $n = 7$) were obtained by Fischer cyclisation [2] of the phenylhydrazone and *p*-tolylhydrazone of *cyclo*nonanone; from the α-naphthylhydrazone of the same ketone, compound (III; $n = 7$) was similarly prepared. *cyclo*Decanone underwent similar cyclisations to give compounds (I; R = H and Me, $n = 8$), and its 6 : 7-benzo-analogue (III; $n = 8$). These *cyclo*alkenoindoles gave violet picrates and red molecular complexes with tetrachlorophthalic anhydride,[3] but all attempts to dehydrogenate the 2 : 3-*cyclo*nonenoindoles with chloranil in boiling xylene or with selenium failed.

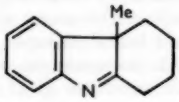
Pfitzinger condensation [4] of *cyclo*octanone, *cyclo*decanone, and *cyclo*nonanone with isatin and 5-substituted isatins afforded, in excellent yields, the 2 : 3-*cyclo*alkenocinchoninic acids (IV). Thermal decomposition of these acids furnished the 2 : 3-*cyclo*alkenoquinolines; here, again, attempts at dehydrogenation of the acids and of the bases were unsuccessful.




(III)




(IV)




(V)

1 : 2 : 3 : 4-Tetrahydro-11-methylcarbazolenine (V), a by-product of the Fischer cyclisation of 2-methyl*cyclo*hexanone phenylhydrazone and described as its yellow picrate,[5] was now prepared crystalline; so was the *cyclo*hexyl analogue, obtained as a by-product in the preparation of 1-*cyclo*hexyl-1 : 2 : 3 : 4-tetrahydrocarbazole.[6] Similar cyclisation of the phenylhydrazones of 2-ethyl-, 2-propyl-, 2-butyl-, 2-hexyl-, and 2-octyl-*cyclo*hexanone afforded the corresponding oily 11-alkyl-1 : 2 : 3 : 4-tetrahydrocarbazolenines, which gave yellow picrates. An attempt to prepare 3-ethyl-2 : 3-*cyclo*pentenoindolenine from the phenylhydrazone of 2-ethyl*cyclo*pentanone gave only impure resins.

* Part XXIII, Buu-Hoï, Jacquignon, and Long, *J.*, 1957, 4994.

[1] Treibs, Steinert, and Kirchhof, *Annalen*, 1953, **581**, 54.
[2] Cf. Buu-Hoï, *J.*, 1949, 2882.
[3] Buu-Hoï and Jacquignon, *Compt. rend.*, 1952, **234**, 1056; *Bull. Soc. chim. France*, 1957, **4**, 488.
[4] Pfitzinger, *J. prakt. Chem.*, 1897, **56**, 283; Buu-Hoï and Royer, *Rec. Trav. chim.*, 1947, **66**, 300.
[5] Plancher, *Atti R. Acad. Lincei*, 1900, **9**, 221; Pausacker and Schubert, *J.*, 1949, 1384.
[6] Buu-Hoï, Binh, Loc, Xuong, and Jacquignon, *J.*, 1957, 3126.

## Experimental

2 : 3-cyclo*Nonenoindole*.—A mixture of *cyclo*nonanone (3 g.) and redistilled phenylhydrazine (3·5 g.) was heated at 120—130°, until steam had ceased to be evolved; the cooled crude phenylhydrazone was treated with a solution of hydrogen chloride in glacial acetic acid (25 c.c.), and the mixture brought to the b. p. After dilution with water, the product was taken up in benzene, the benzene solution washed with water, dried ($Na_2SO_4$), and evaporated, and the residue fractionated. The portion (1·9 g.), b. p. 231—232°/22 mm., $n_D^{29}$ 1·6060, crystallised as colourless prisms, m. p. 65°, from light petroleum (b. p. 35—60°) (Found: C, 84·2; H, 9·1; N, 6·3. $C_{15}H_{19}N$ requires C, 84·5; H, 9·0; N, 6·6%). This *indole* gave a *picrate*, as brown-violet needles, m. p. 110°, from ethanol (Found: N, 12·4. $C_{21}H_{22}O_7N_4$ requires N, 12·7%); the complex with tetrachlorophthalic anhydride formed red needles, m. p. 110°, from acetic acid.

5-*Methyl*-2 : 3-cyclo*nonenoindole*.—Prepared from *cyclo*nonanone (1·5 g.) and *p*-tolylhydrazine (3 g.), this *indole* (0·6 g.), b. p. 224—225°/15 mm., formed colourless prisms, m. p. 110°, from light petroleum (Found: C, 84·3; H, 9·1. $C_{16}H_{21}N$ requires C, 84·5; H, 9·3%); the picrate crystallised as brown-violet needles, m. p. 112°, from ethanol, and the complex with tetrachlorophthalic anhydride as dark red needles, m. p. 147°, from acetic acid.

2 : 3-cyclo*Noneno*-6 : 7-*benzindole*.—Prepared from *cyclo*nonanone (1·5 g.) and α-naphthylhydrazine (4 g.), this *indole* (0·7 g.), b. p. 270—275°/15 mm., formed colourless prisms, m. p. 104°, from *cyclo*hexane (Found: N, 5·2. $C_{19}H_{21}N$ requires N, 5·3%); its picrate crystallised from ethanol as brown-red prisms, m. p. 174° (decomp. >165°).

Attempts were made to dehydrogenate this indole and the two foregoing ones, (*a*) by refluxing for 12 hr. their solution in xylene with chloranil (4 mol.), but gave indole and resins; (*b*) by heating them with selenium at 350°, which resulted in complete decomposition.

2 : 3-cyclo*Decenoindole*.—Prepared from *cyclo*decanone (2 g.) and phenylhydrazine (3 g.), this *indole* (0·8 g.), b. p. 240—245°/26 mm., $n_D^{20}$ 1·6020, crystallised as colourless needles, m. p. 89°, from light petroleum (Found: C, 84·5; H, 9·2; N, 5·9. $C_{16}H_{21}N$ requires C, 84·5; H, 9·3; N, 6·2%). The picrate formed brown-violet needles, m. p. 112°, from ethanol.

5-*Methyl*-2 : 3-cyclo*decenoindole* (1·g.), prepared from *cyclo*decanone (1·5 g.) and *p*-tolylhydrazine (3·5 g.), crystallised as colourless prisms, m. p. 100°, from light petroleum (Found: C, 84·5; H, 9·4; N, 5·5. $C_{17}H_{23}N$ requires C, 84·6; H, 9·5; N, 5·8%); the picrate formed violet-black needles, m. p. 136° (decomp. >128°) from ethanol, and the complex with tetrachlorophthalic anhydride formed red needles (from acetic acid), m. p. 178° (decomp. >170°).

2 : 3-cyclo*Deceno*-6 : 7-*benzindole*.—Prepared from *cyclo*decanone (1·5 g.) and α-naphthylhydrazine (3 g.), this *indole*, b. p. 272—275°/15 mm., formed colourless prisms, m. p. 119°, from *cyclo*hexane (Found: C, 86·8; H, 8·3. $C_{20}H_{23}N$ requires C, 86·6; H, 8·4%) (picrate, brown-violet needles, m. p. 189°, from ethanol; complex with tetrachlorophthalic anhydride, deep red leaflets, m. p. 187°, from acetic acid).

6-*Methyl*-2 : 3-cyclo*octenocinchoninic Acid* (IV; R = Me, *n* = 6).—A mixture of *cyclo*octanone (4 g.), 5-methylisatin (5 g.), and 25% ethanolic potassium hydroxide (20 c.c.) was gently refluxed for 24 hr.; after cooling, water was added, the neutral impurities were removed by ether-extraction, the aqueous layer was acidified with acetic acid, and the precipitate (95%) washed with water, dried, and recrystallised from benzene. The *cinchoninic acid* formed colourless needles, m. p. 354—355° (Found: C, 75·2; H, 6·6; N, 5·2. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%). 6-*Methyl*-2 : 3-cyclo*octenoquinoline* (V; R = Me, *n* = 6), obtained by heating the foregoing acid above its m. p., and distilling the residue *in vacuo*, crystallised as colourless prisms, m. p. 102°, from ethanol (Found: C, 85·0; H, 8·3. $C_{16}H_{19}N$ requires C, 85·3; H, 8·5%); its *picrate* crystallised as yellow prisms, m. p. 185—186°, from ethanol (Found: N, 12·1. $C_{22}H_{22}O_7N_4$ requires N, 12·3%).

Similar reactions gave: 2 : 3-cyclo*nonenocinchoninic acid* (IV; R = H, *n* = 7) (95% yield), prisms, m. p. 313—314° (Found: C, 75·5; H, 6·8; N, 5·5%); 2 : 3-cyclo*nonenoquinoline* (V; R = H, *n* = 7), purified *via* its picrate, yellow needles, m. p. 179—180° (from ethanol), formed prisms, m. p. 55° (Found: N, 5·9%); 6-*methyl*-2 : 3-cyclo*nonenocinchoninic acid* (IV; R = Me, *n* = 7), needles, m. p. 338—339°, from benzene (Found: C, 76·0; H, 7·2. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·5%); 6-*methyl*-2 : 3-cyclo*nonenoquinoline*, prisms, m. p. 79°, from light petroleum (Found: C, 85·1; H, 9·0. $C_{17}H_{21}N$ requires C, 85·3; H, 8·8%) (picrate, yellow prisms, m. p. 183—184°, from ethanol); 2 : 3-cyclo*decenocinchoninic acid* (IV; R = H, *n* = 8) (yield ~100%), needles, m. p. 299°, from ethanol–benzene (Found: C, 75·9; H, 7·4%). 2 : 3-cyclo*Decenoquinoline*, prisms, m. p. 92°, from light petroleum (Found: N, 6·0. $C_{17}H_{21}N$ requires N,

XUM

5·9%); **6-*methyl*-2 : 3-cyclo*decenocinchoninic acid*** (IV; R = Me, *n* = 8) (yield ~100%), needles, m. p. 321—322°, from ethanol–benzene (Found: C, 76·4; H, 7·9; N, 4·7. $C_{19}H_{23}O_2N$ requires C, 76·7; H, 7·8; N, 4·7%); **6-*methyl*-2 : 3-cyclo*decenoquinoline***, prisms, m. p. 93° (light petroleum) (Found: C, 85·3; H, 9·3. $C_{18}H_{23}N$ requires C, 85·3; H, 9·2%) (picrate, yellow needles, m. p. 202°, from ethanol).

**1 : 2 : 3 : 4-*Tetrahydro*-11-*methylcarbazolenine*** (V; R = Me).—A mixture of 2-methyl*cyclo*hexanone (10 g.) and phenylhydrazine (10 g.) was heated at 120° with removal of steam, and the crude phenylhydrazone cyclised with a solution of hydrogen chloride in glacial acetic acid in the usual way; the product was then diluted with water, and the oil obtained on basification was taken up in benzene and purified by distillation *in vacuo*. The carbazolenine, purified *via* its yellow picrate, m. p. 174° (lit., 169—171°), had b. p. 158°/20 mm., $n_D^{21}$ 1·5672, which crystallised as prisms, m. p. 69°, from light petroleum (Found: N, 7·3. Calc. for $C_{13}H_{15}N$: N, 7·5%). **11-cyclo*Hexyl*-1 : 2 : 3 : 4-*tetrahydrocarbazolenine***, prepared in the same way from phenylhydrazine and 2-*cyclo*hexyl*cyclo*hexanone, and purified *via* its *picrate*, yellow prisms, m. p. 185° (Found: N, 11·3. $C_{24}H_{26}O_7N_4$ requires N, 11·6%), formed colourless prisms, m. p. 82°, from light petroleum (Found: C, 85·1; H, 9·0. $C_{18}H_{23}N$ requires C, 85·3; H, 9·2%). The other carbazolenines (see Table) were similarly prepared, in 30—40% yield.

**11-*Alkyl*-1 : 2 : 3 : 4-*tetrahydrocarbazolenines*** (V).

| Alkyl | B. p./mm. (m. p.) | Formula | N (%), Found | N (%), Reqd. |
|---|---|---|---|---|
| Et | 161°/18 | $C_{14}H_{17}N$ | 6·9 | 7·0 |
| Picrate | M. p. 146° | $C_{20}H_{20}O_7N_4$ | 12·8 | 13·1 |
| Pr | 178°/28 | $C_{15}H_{19}N$ | 6·8 | 6·6 |
| Picrate | M. p. 139° | $C_{21}H_{22}O_7N_4$ | 12·5 | 12·7 |
| Bu | 189°/22 mm. | $C_{16}H_{21}N$ | 6·2 | 6·2 |
| Picrate | M. p. 130° | $C_{22}H_{24}O_7N_4$ | 12·0 | 12·3 |
| Hexyl picrate | M. p. 135° | $C_{24}H_{28}O_7N_4$ | 11·3 | 11·6 |
| Octyl picrate | M. p. 124° | $C_{26}H_{32}O_7N_4$ | 10·7 | 10·9 |

This investigation was supported in part by a research grant from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service; the authors thank the authorities concerned.

The Radium Institute, The University of Paris. [*Received, October 9th*, 1957.]

---

## 144. *The Synthesis of Some Galactaric (Mucic) Acid Derivatives.*

By K. Butler, D. R. Lawrance, and M. Stacey.

The synthesis of some acetal, ketal, and acyl derivatives of galactaric acid is described.

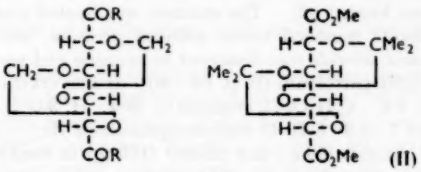
In the course of a survey of polyamide intermediates derived from carbohydrates, several novel derivatives of galactaric acid have been prepared. The acid was of interest because it is potentially available from natural sources such as lactose and fruit pectin and its hydroxyl groups are symmetrically disposed. Earlier work by Haworth, Heath, and Wiggins [1] on other hexaric acids established that inactivation of the hydroxyl groups during polymerisation was essential if linear polymers were to be made. Acylation, ketal, and acetal formation afford possible methods of protection and these have been studied in our experiments.

A dimethylene derivative of mucic acid has been described by Lobry de Bruyn and van Ekenstein.[2] Its melting point, the only characteristic reported, does not agree with our value and this derivative may have a different arrangement of acetal rings. In this respect it should be noted that the orientation of the methylene and *iso*propylidene groups assigned to the compounds described here has not been established. However, if the rules

[1] Haworth, Heath, and Wiggins, *J.*, 1944, 155.
[2] Lobry de Bruyn and van Ekenstein, *Rec. Trav. chim.*, 1902, **21**, 316.

postulated by Barker, Bourne, and Whiffen [3] for acetal rings in polyhydric alcohols are applicable to acetal and ketal derivatives of hexaric acids, the groups should bridge positions 2 : 4 and 3 : 5. It is known that reduction of our dimethyl di-*O*-methylenegalactarate gives a di-*O*-methylenedulcitol identical with one derived from 1 : 6-di-*O*-benzoyldulcitol.[4] We have therefore provisionally assigned the 2 : 4-3 : 5-structure to dimethyl di-*O*-methylenegalactarate on the assumption that the alcohol itself is not an exception to the rules and that the acetal rings do not assume a different configuration during the reduction.

(I): R = OMe.
(Ia): R = OH.
(Ib): R = Cl.
(Ic): R = OPh.
(Id): R = OEt.
(Ie): R = O·$CH_2$·CH:$CH_2$.
(If): R = $NH_2$.



(II)

Attempts to remove the cyclic acetal groups in dimethyl 2 : 4-3 : 5-di-*O*-methylenegalactarate by acid hydrolysis showed them to be extremely stable and to require boiling 12N-sulphuric acid for complete hydrolysis. The ketal groups in dimethyl di-*O*-*iso*propylidenegalactarate, however, proved to be more labile and were completely removed in either dilute mineral acid or 80% acetic acid.

Polymerisation of some of these galactaric acid derivatives with straight-chain diamines has given fibre-forming polyamides.[5]

## Experimental

*Dimethyl Galactarate.*—A suspension of galactaric acid (210 g.) in B.S.S.-grade methanol (1 l.) containing concentrated sulphuric acid (15 ml.) was heated under reflux for 3—4 days. The mixture was left overnight at 0° and the crystalline product (218 g., 96%), m. p. 186—188° (decomp.), was filtered off, washed with water, and dried. The crude ester was usually contaminated with a small quantity of galactaric acid but was sufficiently pure for the preparation of dimethyl 2 : 4-3 : 5-di-*O*-methylenegalactarate. Pure dimethyl galactarate, m. p. 196—198° (decomp.) [lit.,[6] 205° (decomp.)], could be obtained by recrystallisation of the above product from boiling methanol (Found: C, 40·4; H, 5·9. Calc. for $C_8H_{14}O_8$: C, 40·3; H, 5·9%).

*Dimethyl* 2 : 4-3 : 5-*Di*-O-*methylenegalactarate* (I).—The method used for the preparation of dimethyl di-*O*-methylene-D-glucosaccharate [7] was applied with modifications. A stirred mixture of dimethyl galactarate (205 g.), paraformaldehyde (103 g.), and concentrated sulphuric acid (80 ml.) was heated at 75—80° for 20—30 min. The melt was allowed to cool, methanol (900 ml.) added, and the mixture heated under reflux for 6 hr. After hot filtration to remove unchanged paraformaldehyde the filtrate was cooled and dimethyl 2 : 4-3 : 5-di-*O*-methylenegalactarate, together with some dimethyl galactarate, was precipitated. The product was filtered off and dried. The methylene derivative was purified by extraction with dry chloroform at room temperature, the insoluble dimethyl galactarate being removed by filtration. After removal of solvent under reduced pressure the residue was crystallised from methanol, to give *dimethyl* 2 : 4-3 : 5-*di*-O-*methylenegalactarate* (113 g., 50%), m. p. 106—107° (Found: C, 45·8; H, 5·3. $C_{10}H_{14}O_8$ requires C, 45·8; H, 5·3%). Note: The insoluble dimethyl galactarate could be recycled to give an overall yield of 64% of the methylene derivative.

2 : 4-3 : 5-*Di*-O-*methylenegalactaric Acid* (Ia).—Aqueous barium hydroxide was used to hydrolyse the ester groups as in the preparation of di-*O*-methylene-D-glucosaccharic acid.[7] Barium hydroxide octahydrate (124 g.) was added to a hot aqueous solution (1750 ml.) of

[3] Barker, Bourne, and Whiffen, *J.*, 1952, 3865.
[4] Butler and Cummings, *J.*, 1956, 636.
[5] B.P. 750,822.
[6] Holleman, *Rec. Trav. chim.*, 1898, **17**, 326.
[7] Haworth, Jones, Stacey, and Wiggins, *J.*, 1944, 61.

dimethyl 2 : 4-3 : 5-di-*O*-methylenegalactarate (60·5 g.), and the mixture maintained at 80° for 90 min. The barium salt of the acid was decomposed with aqueous sulphuric acid (27·9 ml.; 1 : 1 v/v), the mixture was boiled for 15 min., then filtered hot, and the aqueous filtrate taken down to dryness under reduced pressure. The residue recrystallised from boiling water, giving 2 : 4-3 : 5-*di*-O-*methylenegalactaric acid* as a highly crystalline monohydrate (52·4 g., 96%), m. p. (anhydrous) 180—182° (decomp.) (Found: C, 40·8; H, 4·4. $C_8H_{10}O_8$ requires C, 40·9; H, 4·3%).

2 : 4-3 : 5-*Di*-O-*methylenegalactaroyl Chloride* (Ib).—Anhydrous, finely powdered 2 : 4-3 : 5-di-*O*-methylenegalactaric acid (40 g.) was suspended in thionyl chloride (220 ml.; freshly distilled from linseed oil). The mixture was heated under gentle reflux for 6 hr. and excess of thionyl chloride removed under reduced pressure, leaving a thick syrup which crystallised. The crude *acid chloride* was dissolved in benzene and reprecipitated by the addition of an equal volume of light petroleum (b. p. 60—80°) as fine crystals (42 g., 83%), m. p. 70—72° (Found: C, 35·4; H, 3·4. $C_8H_8O_6Cl_2$ requires C, 35·4; H, 3·0%).

*Diphenyl* 2 : 4-3 : 5-*Di*-O-*methylenegalactarate* (Ic).—A solution of 2 : 4-3 : 5-di-*O*-methylenegalactaroyl chloride (60 g.) and phenol (120 g.) in freshly distilled, dry pyridine (300 ml.) was heated under reflux for 2 hr. The solution was cooled and kept at 0° for 12 hr., then poured into iced water (2—3 l.), the *diphenyl ester* being precipitated. The crude ester was thoroughly washed with ether and dried (40·5 g.). Decolorising with charcoal and two recrystallisations from benzene–light petroleum (b. p. 60—80°) afforded fine needles (36·5 g., 43%), m. p. 143—145° (Found: C, 62·1; H, 4·6. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%).

*Diethyl Galactarate*.—This compound, m. p. 168—169°, was prepared from galactaric acid as described by Tipson and Clapp,[8] in 77% yield.

*Diethyl* 2 : 4-3 : 5-*Di*-O-*methylenegalactarate* (Id).—A stirred mixture of diethyl galactarate (21·5 g.), paraformaldehyde (10 g.), and concentrated sulphuric acid (7 ml.) was heated on a water-bath at 75° for 20 min. The solution was allowed to cool, absolute ethanol (75 ml.) added, and the mixture heated under reflux for 4 hr. The solution was concentrated to half volume and filtered hot. A crystalline product (11·1 g.) was deposited on cooling. The alcoholic mother-liquor was concentrated to about 25 ml., an equal volume of ether added, and the mixture kept at 0° for 12 hr.: a further crop (1·2 g.) was deposited. The combined crops were purified by extraction with dry chloroform (50 ml.) at room temperature and the insoluble diethyl galactarate (1·4 g.) was filtered off. The chloroform solution was taken down to dryness and the residue after recrystallisation from absolute ethanol afforded *diethyl* 2 : 4-3 : 5-*di*-O-*methylenegalactarate* (6·1 g., 24%), m. p. 68—69° (Found: C, 50·1; H, 6·2. $C_{12}H_{18}O_8$ requires C, 49·8; H, 6·2%).

*Diallyl* 2 : 4-3 : 5-*Di*-O-*methylenegalactarate* (Ie).—Finely powdered 2 : 4-3 : 5-di-*O*-methylenegalactaric acid (5 g.) was suspended in 1% allyl-alcoholic hydrogen chloride (30 ml.) and boiled gently under reflux for 10 hr., the acid slowly dissolving. The solution was neutralised with lead carbonate (*ca.* 10 g.) and filtered. The filtrate was evaporated to dryness, leaving a syrup which rapidly crystallised. Recrystallisation from methanol afforded fine needles of the *diallyl ester* (4·4 g., 66%), m. p. 63·5° (Found: C, 53·5; H, 5·8. $C_{14}H_{18}O_8$ requires C, 53·5; H, 5·8%).

*Dimethyl* 2 : 4-3 : 5-*Di*-O-iso*propylidenegalactarate* (II).—Dry, finely powdered dimethyl galactarate (30 g.) was suspended in dry acetone (2 l.) containing hydrogen chloride (20 g.). The mixture was heated under gentle reflux until dissolution was complete (*ca.* 2 hr.). The solution was cooled, made alkaline (pH 8—9) with 3% sodium carbonate solution (*ca.* 600 ml.), and extracted with chloroform (3 × 500 ml.). The combined extracts were dried ($MgSO_4$) and the solvent was removed. The residual syrup crystallised at 0°. The iso*propylidene derivative* (11·3 g., 31%), m. p. 97—98°, recrystallised from methanol (Found: C, 52·9; H, 6·8. $C_{14}H_{22}O_8$ requires C, 52·8; H, 6·9%).

2 : 4-3 : 5-*Di*-O-*methylenegalactaramide* (If).—A stirred, ice-cold suspension of finely powdered dimethyl 2 : 4-3 : 5-di-*O*-methylenegalactarate (50 g.) in dry methanol (1 l.) was saturated with ammonia and set aside at 0° for 12 hr. The crystalline product was filtered off and washed with methanol. Recrystallisation from water gave 2 : 4-3 : 5-*di*-O-*methylenegalactaramide* (43 g., 97%), m. p. 215° (decomp.) (Found: C, 41·3; H, 5·4; N, 12·2. $C_8H_{12}O_6N_2$ requires C, 41·3; H, 5·2; N, 12·1%).

*Hydrolysis of the Acetal Groups in Dimethyl* 2 : 4-3 : 5-*Di*-O-*methylenegalactarate*.—Three

[8] Tipson and Clapp, *J. Org. Chem.*, 1953, **18**, 952.

samples of ester (0·5 g.) were dissolved in three aliquot parts (100 ml.) of 3N-, 6N-, and 12N-sulphuric acid. The solutions were heated under steam-distillation conditions (so that the concentration of the acid remained constant during the hydrolysis) for 45 min. The liberated formaldehyde was collected in a water-trap and estimated by the sodium sulphite method.[9] The results are summarised in the Table.

| Strength of acid used | 3N | 6N | 12N |
|---|---|---|---|
| Formaldehyde evolved (%) | 1·3 | 10·2 | 22·9 |
| Theor. available formaldehyde | | 22·96% | |

Attempted hydrolysis by glacial acetic acid, 80% acetic acid, or 5% phosphoric acid was unsuccessful.

*Hydrolysis of the Ketal Groups in Dimethyl* 2 : 4-3 : 5-*Di*-O-iso*propylidenegalactarate*.—The ester (0·5 g.) in N-sulphuric acid (12·5 ml.) was heated under reflux for 1 hr. The solution was kept at 0° overnight and the precipitated galactaric acid filtered off and dried [0·28 g., 85%; m. p. 209—211° (decomp.); lit.,[10] 206° (decomp.)] (Found: C, 34·3; H, 5·1. Calc. for $C_6H_{10}O_8$: C, 34·2; H, 4·8%). A similar result was obtained on using 80% acetic acid as hydrolytic reagent.

*Dimethyl* 2 : 3 : 4 : 5-*Tetra*-O-*benzoylgalactarate*.*—Finely powdered dimethyl galactarate (1·0 g.), suspended in dry pyridine (10 ml.), was left with freshly distilled benzoyl chloride (2 ml.) at room temperature for 60 hr. The solid product was filtered off, washed with water, and dried. Crystallisation from methanol gave *dimethyl* 2 : 3 : 4 : 5-*tetra*-O-*benzoylgalactarate* (1·3 g., 49·1%), m. p. 167—169° (Found: C, 65·8; H, 4·8. $C_{36}H_{30}O_{12}$ requires C, 66·1; H, 4·6%).

2 : 3 : 4 : 5-*Tetra*-O-*acetylgalactaroyl Chloride*.—This compound, m. p. 181°, was prepared as described by Müller,[12] in 73% yield.

*Diphenyl* 2 : 3 : 4 : 5-*Tetra*-O-*acetylgalactarate*.—A mixture of 2 : 3 : 4 : 5-tetra-*O*-acetylgalactaroyl chloride (10·4 g.) in dry benzene (100 ml.) and phenol (4·9 g.) was heated under reflux for 48 hr. The solution was cooled and the precipitated ester filtered off. Recrystallisation from benzene afforded fine needles of the *diphenyl ester* (8·7 g., 73%), m. p. 168° (Found: C, 58·7; H, 5·0. $C_{26}H_{26}O_{12}$ requires C, 58·8; H, 4·9%).

The authors thank Mr. N. J. Miles for assistance with the experimental work, and British Nylon Spinners, Limited, for permission to publish these results.

RESEARCH DEPARTMENT, BRITISH NYLON SPINNERS, LIMITED,
PONTYPOOL, MONMOUTHSHIRE.
THE CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, June 14th*, 1957.]

* Since this paper was written this compound has been reported by Baelor and Gorin.[11]

[9] Lemme, *Chem.-Ztg.*, 1903, **27**, 896.
[10] Tollens and Kent, *Annalen*, 1885, **227**, 221.
[11] Baelor and Gorin, *J. Org. Chem.*, 1957, **22**, 65.
[12] Müller, *Ber.*, 1914, **47**, 2654.

XUM

## 145. *Antimony Halides as Solvents. Part I. Cryoscopic Data in Antimony Trichloride.*

By G. B. Porter and E. C. Baughan.

Cryoscopic measurements in antimony trichloride (m. p. 73·17°) are presented which extend and confirm Tolloczko's pioneer work.[1] From solutions of fluorene, dibenzyl, benzophenone, and anthracene the cryoscopic constant has been determined and corrected for non-ideality.

Tetramethylammonium and triphenylmethyl chlorides are strong electrolytes, while cæsium and potassium chlorides are completely dissociated only at infinite dilution (cf. the conductivity data of Klemensiewicz *et al.*[2c]). The osmotic coefficients for these electrolytes can be interpreted in terms of solvation and ion-pair formation by comparison with the Debye–Hückel equation.

Stilbene dimerises completely, and the dimer has been isolated.

The study of non-aqueous ionising solvents [3] has produced many important chemical results; work on sulphuric acid and liquid ammonia, for example, has greatly extended our knowledge of proton acids and bases by providing equilibrium data on many systems previously unknown or inferred from kinetic measurements. The extension of such information to ions produced in ways other than by protonation is therefore desirable. The necessary properties of such solvents are (*a*) the ability to promote ionisation by solvation, just as the formation of $OH_3^+$ in water or of $NH_4^+$ in ammonia assists the ionisation of proton acids; (*b*) a high dielectric constant, since otherwise conductivities are almost uninterpretable through ion-association; and (*c*) a convenient melting-point, to permit determination of the number of ions formed by a solute molecule, and also of the activity data necessary for thermodynamic studies.

We investigated liquid antimony trichloride (f. p. 73·2°), chosen since pioneer work in Poland on freezing-point depressions [1] and conductivities [2] has shown that it is a good ionising solvent. In particular, Klemensiewicz and Balówna [2c] measured the conductivities at 99° of several halides in dilute solution; their results give linear Kohlrausch plots as can be seen in Fig. 1, which also shows the theoretical Debye–Hückel–Onsager slopes. In calculating these, we assumed that the viscosity and dielectric constant at 99° are 1·84 centipoises and 30·4 respectively. The former was estimated from Klemensiewicz's viscosity–temperature data [2a] by interpolation, by use of Batschinski's equation,[4] and the latter from Schlundt's value [5] of 33·2 at 75°, by using Onsager's equation [6] relating dielectric constant to dipole moment. We see not only that the interionic effects on conductivity are as expected for a solvent of such a dielectric constant (cf. methanol and ethanol [7]), but also that all the limiting conductivities are almost identical. This suggests that chloride and bromide ions have abnormally high mobilities, and agrees with the high transport numbers (about 0·9) obtained for the chloride ion in ammonium and potassium chloride solutions by Tolloczko.[8] Abnormal mobilities imply favourable rates [9] for such processes as

$$OH_3^+ + OH_2 \longrightarrow OH_2 + OH_3^+$$

and therefore (probably)

$$SbCl_4^- + SbCl_3 \longrightarrow SbCl_3 + SbCl_4^-$$

[1] Tolloczko, (*a*) *Z. phys. Chem.*, 1899, **30**, 705; (*b*) *Bull. int. Acad. Sci. Cracovie*, 1901, **1**, 1.

[2] (*a*) Klemensiewicz, *Bull. int. Acad. Sci. Cracovie*, 1908, **6**, 485; (*b*) *idem*, *Z. phys. Chem.*, 1924, **113**, 28; (*c*) Klemensiewicz and Balówna, *Roczniki Chem.*, 1930, **10**, 481; (*d*) *idem*, *ibid.*, 1931, **11**, 683; (*e*) Klemensiewicz and Zebrowska, *ibid.*, 1934, **14**, 14.

[3] Gutmann, *Quart. Rev.*, 1956, **10**, 451.

[4] Batschinski, *Z. phys. Chem.*, 1913, **84**, 643.

[5] Schlundt, *J. Phys. Chem.*, 1901, **5**, 503.

[6] Onsager, *J. Amer. Chem. Soc.*, 1936, **58**, 1486.

[7] Murray-Rust, Gatty, MacFarlane, and Hartley, *Ann. Reports*, 1930, **27**, 326.

[8] Frycz and Tolloczko, *Festschrift Univ. Lwów*, 1912, **1**, 1; *Chem. Zentr.*, 1913, I, 91.

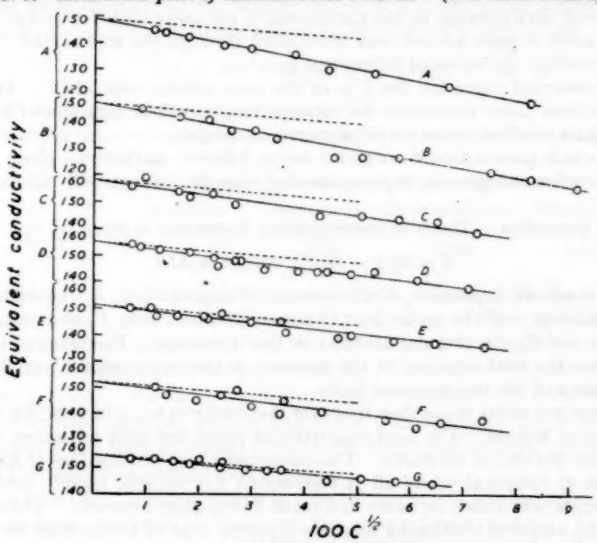
[9] Baughan, quoted in Glasstone, Laidler, and Eyring, "The Theory of Rate Processes," McGraw-Hill, New York, 1941, p. 568—575.

with chemical solvation of the ions concerned. A high transport number (0·88—0·97) has also been reported [10] for chloride ions in solutions of tetramethylammonium chloride in arsenic trichloride. This solvent has a lower dielectric constant [5] (12·35 at 21°), and the solubility of alkali-metal chlorides is less than in antimony trichloride, in which only lithium and sodium chlorides are insoluble.[2a]

Antimony trichloride thus seems to fulfil all three of our criteria better than the other metal halides recently investigated.[3] In addition, the chemistry of this solvent is remarkable; it is a " Lewis acid " and therefore a Friedel–Crafts catalyst, and gives colour reactions with conjugated hydrocarbons, such as the standard test for vitamin A, although these appear to be due to traces of antimony pentachloride.[11]

The results reported here show that normal solutes can be found, and that salts show activity effects of the magnitude to be expected; the earlier Polish work is confirmed wherever overlap occurs.

FIG. 1. *Kohlrausch plots of Klemensiewicz's results* [2c] (*C is solute molarity*).




---- Limiting Onsager slopes.

*A*, TlCl; *B*, TlBr; *C*, KCl; *D*, KBr; *E*, $NH_4Cl$; *F*, $NH_4Br$; *G*, RbCl.

## EXPERIMENTAL

*Materials.*—" AnalaR " antimony trichloride was repeatedly distilled under reduced pressure in a current of dry, oxygen-free nitrogen. Anthracene (B.D.H. " blue fluorescence ") and the other hydrocarbons were recrystallised; benzophenone was vacuum-distilled. Tetramethylammonium chloride was prepared by neutralisation of the hydroxide (25% aqueous solution), and was recrystallised from ethanol; tetramethylammonium bromide was recrystallised from methanol. Both salts were dried at 120°, and their purity was checked by halide analysis. Potassium and cæsium chlorides (" AnalaR ") were dried at 300°. Triphenylmethyl chloride was recrystallised from light petroleum (b. p. 60—80°) containing 10% of acetyl chloride.

*Measurement of Freezing Points.*—The apparatus was a conventional Beckmann freezing-point cell, suitably modified to prevent access of moisture, and tapered at the bottom to prevent breakage (since antimony chloride expands considerably on melting). The ground-on head of the cell carried a mercury-sealed stirrer with a Polythene stopper, and three standard ground joints, which accommodated respectively a Beckmann thermometer, a drying-tube containing

[10] Gutmann, *Svensk Kem. Tidskr.*, 1956, **68**, 1.
[11] Brüggemann, Krauss, and Tiews, *Chem. Ber.*, 1952, **85**, 315.

XUM

" Anhydrone " (magnesium perchlorate), and an inlet for nitrogen. The thermometer could be read to $\pm 0{\cdot}001°$, and was calibrated at the National Physical Laboratory. All joints were lubricated with Silicone stop-cock grease. Solutes were introduced, from a device similar to that described by Newman *et al.*,[12] by removing the drying-tube while dry nitrogen was being passed through the apparatus. During measurements the cryoscope was placed in an air jacket in an oil thermostat at 1·5—2·5° below the f. p.

About 15 ml. of the purified antimony trichloride were redistilled directly into the lower half of the cryoscope, a small fore-run being rejected. The distillation apparatus was then placed in a glove-box under a positive pressure of dry nitrogen, and the cell detached, sealed with a ground-glass cap, weighed, and replaced in the dry-box, where the solvent was carefully melted and the top of the cell was fitted.

For each determination the apparatus was kept in an auxiliary oil bath at about 95° until the antimony trichloride had melted, and was then transferred to the thermostat. The freezing-point of the pure solvent was recorded at once, but after each addition of solute, the cryoscope was kept in the thermostat for at least 1 hr., to ensure complete solution. It was then reheated for a few minutes in the auxiliary bath (in case crystallisation had occurred), removed, and allowed to cool, with stirring, in the thermostat to not more than 1·5° below the f. p., whereupon a small crystal of pure solvent was introduced through the solute inlet. In many cases spontaneous crystallisation occurred before this point.

The highest observed value for the f. p. of the pure solvent was 73·17°. On any one day, the f. p. of a solution (after correction for supercooling) could be reproduced to within 0·005°, although sometimes a fall of about 0·010° occurred overnight.

The solutes which gave coloured solutions are as follows: anthracene (deep green), fluorene (deep blue), benzophenone (green), triphenylmethyl chloride (orange-red), dibenzyl and stilbene (pale green).

*Supercooling Correction.*—The true freezing-point depression is given by [13]

$$\theta = \theta_1[1 - (n_1C_p + C_0)S/n_1\Delta H_0^f]$$

where $\theta_1$ is the observed depression, $S$ the amount of supercooling, $n_1$ the number of moles of solvent in the solution, $\Delta H_0^f$ the molar heat of fusion of the solvent, $C_p$ the molar heat capacity of liquid solvent, and $C_0$ the thermal capacity of the cryoscope. The main contribution to the small $C_0$ term was the heat capacity of the mercury in the thermometer, which was estimated from the dimensions of the thermometer bulb.

This correction was never more than 0·02° for non-electrolytes, and 0·04° for the electrolytes.

*Heat Capacity of Solvent.*—The heat capacities of fused and solid antimony trichloride were determined by the method of mixtures. The calorimeter was a small Dewar flask containing a constant amount of technical white oil (a convenient non-volatile liquid), and the sample of antimony trichloride was sealed *in vacuo* in a small Pyrex glass ampoule. The calorimeter was calibrated with an ampoule containing mercury (specific heat of Pyrex from de Vries [14]). The resultant mean heat capacities were 33·3 cal. mole$^{-1}$ deg.$^{-1}$ over the range 76—98° for the liquid solvent (mean of six experiments), and 25·8 cal. mole$^{-1}$ deg.$^{-1}$ over the range 28—69° for the solid solvent (three experiments). These values are sufficiently precise for the small correction terms needed in the reduction of the observations; we would draw attention to the unusually large change in specific heat on melting. We have found no previous data except the value 25·1 cal. mole$^{-1}$ deg.$^{-1}$ for the mean heat capacity of the solid between 0° and 33° obtained by Pebal and Jahn [15] with an ice calorimeter.

## Results and Discussion

The cryoscopic equation [16] is, as far as terms in $\theta^2$,

$$\theta(1 + \alpha\theta) = -m_1k_f \ln a_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where

$$\alpha = \frac{1}{T_0} - \frac{\Delta C_p}{2\Delta H_0^f}; \; k_f = \frac{RT_0^2}{m_1\Delta H_0^f}$$

[12] Newman, Kuivila, and Garrett, *J. Amer. Chem. Soc.*, 1945, **67**, 704, Fig. 1*a*.
[13] Gold, Hawes, and Tye, *J.*, 1952, 2170.
[14] de Vries, *Ind. Eng. Chem.*, 1930, **22**, 617.
[15] von Pebal and Jahn, *Wied. Ann.*, 1886, **27**, 584.
[16] Lewis and Randall, " Thermodynamics," McGraw-Hill, New York, 1923, p. 282.

$\Delta H_0^f$ is the heat of fusion of pure solid solvent at its melting point $T_0$, $\Delta C_p$ the difference between the heat capacities of the liquid and solid solvent, $m_1$ the molality of the solvent in the solution, $k_f$ the cryoscopic constant, and $a_1$ the activity of the solvent at the freezing point of the solution.

I. *Non-electrolytes.*—Anthracene, fluorene, benzophenone, and dibenzyl give identical depressions in dilute solution and are therefore normal solutes, although the intense colours of their solutions and the marked negative deviations of the freezing-point depressions from Raoult's law showed that there was some interaction with the solvent. Allowance can be made for this interaction, without specifying its nature, by the following semi-empirical treatment.

For a solution of a non-electrolyte, $a_1 = N_1 f_1$, where $N_1$ and $f_1$ are respectively the mole fraction and activity coefficient of the solvent. For many binary systems [17]

$$\ln f_1 = \beta N_2^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where $N_2$ is the mole fraction of the solute, and $\beta$ is a constant at a given temperature. Therefore, since $\ln N_1 \sim -N_2$ for dilute solutions, we can write eqn. (1) as

$$\theta(1 + \alpha\theta) = m_1 k_f (N_2 - \beta N_2^2) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $m_1 = 4{\cdot}38$ mole kg.$^{-1}$ for antimony trichloride.

This equation was fitted to our results by the least-squares method (Table 1).

TABLE 1. *Results of least-squares calculations.*

| | Fluorene | Anthracene | Benzophenone | Dibenzyl | Stilbene |
|---|---|---|---|---|---|
| $k_f$ (deg. mole$^{-1}$ kg.) ..... | 16·7 | 15·5 | 15·2 | 15·0 | 7·89 |
| $\beta$ ..... | −4·11 | −3·20 | −4·28 | −7·57 | −5·43 |

The mean value of $k_f$ is $15{\cdot}6 \pm 0{\cdot}2$ deg. mole$^{-1}$ kg., which, with $T_0 = 346{\cdot}3°$ K, gives $\Delta H_0^f = 3485$ cal. mole$^{-1}$ and $\alpha = 0{\cdot}0018$ deg.$^{-1}$. In Fig. 2 the experimental values of $\theta(1 + 0{\cdot}0018\theta)$ are plotted against $N_2$, and the curves have been calculated from eqn. (3) with the appropriate values of $k_f$ and $\beta$ (Table 1). Tolloczko [18] reported a considerably higher value for $k_f$ (18·4). As can be seen from Fig. 2, his points lie somewhat higher than our own, but show more scatter, and no correction was made for deviation from Raoult's law; a value of 17·9 has been obtained [18] from the difference in heats of solution in hydrochloric acid of the solid and supercooled liquid.

It is evident from Fig. 2 that stilbene is exactly dimerised in this solvent; its value for $k_f$ has therefore been doubled in assessing the mean figure above. The experimental points are from two independent runs. Dimerisation occurred within the time taken for the solvent to melt, as no intermediate depressions were ever observed. The dimer was recovered from solution, and resembled the products obtained from the isomeric stilbenes and sulphuric acid by Brackman and Plesch,[19] who suggested that their dimers were mainly 3-benzyl-1 : 2-diphenylindane.

*Isolation of stilbene dimer.* The dimer was recovered as a colourless, transparent resin (in almost quantitative yield) by dissolving the solidified melt in benzene, extracting the antimony trichloride with hydrochloric acid, and evaporating the benzene *in vacuo*. It was slowly deposited from alcoholic solution as an amorphous, granular solid, which had a melting transition of 45—70° [Found: C, 93·2; H, 6·7%; *M* (cryoscopic in benzene), 363. $(C_{14}H_{12})_2$ requires C, 93·3; H, 6·7%; *M*, 360]. The substance was unaffected by fractional crystallisation, it would not undergo addition reactions with bromine or potassium permanganate, and the infrared spectrum showed none of the bands characteristic of olefinic double bonds.

[17] Hildebrand and Scott, "The Solubility of Non-Electrolytes," Reinhold Publishing Corp., New York, 1950, p. 35.
[18] Tolloczko and Meyer, *Kosmos*, 1910, **35**, 641; *Chem. Abs.*, 1911, **5**, 1881.
[19] Brackman and Plesch, *J.*, 1953, 1289.

XUM

II. *Electrolytes.*—In Fig. 3 we show our results for the electrolytes and those of Tolloczko [15] for potassium chloride as van't Hoff *i*-factors, calculated (in both cases) from the relation $i = \theta/15{\cdot}6m_2$, where $m_2$ is the molality of the solute. It is clear that the

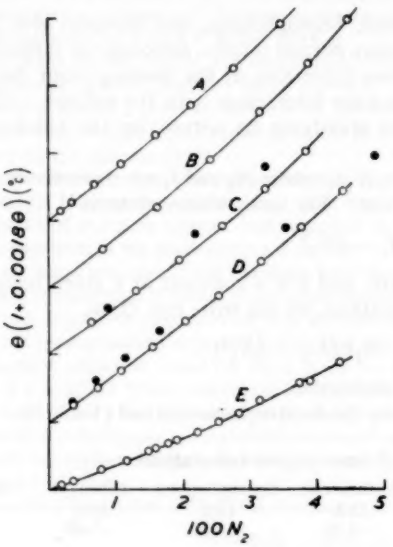



FIG. 2. *Freezing-point depressions produced by non-electrolytes.*
The curves are separated vertically by 1° at their origins.
——— Calculated from eqn. (3).
●, Tolloczko [15] (*C* and *D*).
○, present investigation.
*A*, fluorene.
*B*, dibenzyl.
*C*, benzophenone.
*D*, anthracene.
*E*, stilbene.

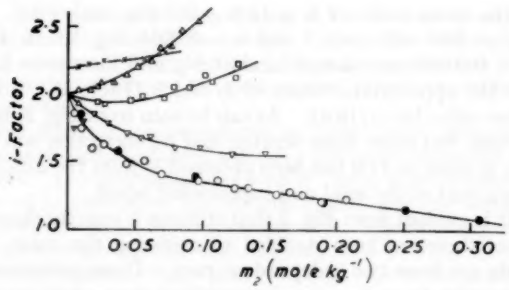



FIG. 3. *i-Factors for electrolytes.*
×, $Me_4NBr$.
△, $Ph_3CCl$.
□, $Me_4NCl$.
▽, CsCl.
○, KCl (present work).
●, KCl (Tolloczko [15]).

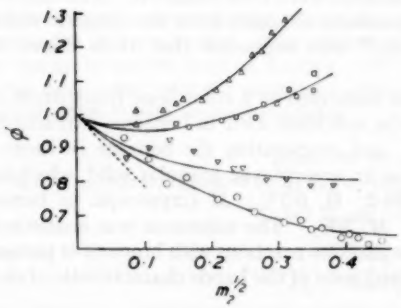



FIG. 4. *Comparison of experimental osmotic coefficients with eqn.* (10).
– – – – Limiting Debye–Hückel slope (eqn. 9).
——— Calc. from eqn. (10) with following values of *d* and *b*

| | *d* | *b* |
|---|---|---|
| △ $Ph_3CCl$ ..... | 15 | 3·1 |
| □ $Me_4NCl$ ..... | 13 | 1·1 |
| ▽ CsCl ..... | 4·5 | 0 |
| ○ KCl ..... | 2·1 | 0 |

*i*-factors for the chlorides tend to the obvious value 2 at infinite dilution. Antimony trichloride is however the only solvent yet investigated in which triphenylmethyl chloride is a strong electrolyte. Thus, the ebullioscopic *i*-factor for this solute in liquid sulphur

dioxide [20] is less than 2 (approaching this value in very dilute solutions), while in nitromethane, it has been shown spectrophotometrically [21] that the chloride exists only as ion-pairs, which dissociate partially when mercuric chloride is added.

The following discussion shows that the general form of the curves in Fig. 3 agrees with the usual extensions to the Debye–Hückel osmotic theory. Tetramethylammonium bromide must be excluded, however, as this solute has a limiting *i*-factor of 2·2, which may be the result of partial halogen exchange, *e.g.*,

$$Me_4NBr + SbCl_3 \rightleftharpoons Me_4N^+ + Cl^- + SbCl_2Br$$

Such an exchange would not, however, invalidate the conductivity data of Klemensiewicz [2c] on bromides. Similarly, although Gutmann [22] mentions that tetramethylammonium iodide reacts slowly with the solvent arsenic trichloride, he found that the conductivities of "freshly prepared" solutions agreed closely with the Onsager limiting equation for this solvent.

*Osmotic coefficients.* The most convenient way of expressing the non-ideality of electrolyte solutions from freezing-point data is in terms of the molal osmotic coefficient, $\phi$, defined by eqn. (4), where $\nu$ is the number of ions produced by one molecule of solute, and

$$\ln a_1 = -\nu\phi m_2/m_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$m_2$ is the molality of the solute. Substituting this expression in equation (1), we obtain eqn. (5) for a solution of an electrolyte.

$$\theta(1 + \alpha\theta) = \nu\phi k_f m_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

If we insert the values $\alpha = 0{\cdot}0018$ deg.$^{-1}$, $k_f = 15{\cdot}6°$ mole$^{-1}$ kg., and $\nu = 2$ (for a symmetrical electrolyte), eqn. (5) becomes eqn. (6).

$$\theta(1 + 0{\cdot}0018\theta) = 31{\cdot}2\phi m_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

In Fig. 4, experimental values of $\phi$, calculated from eqn. (6) are plotted against $m_2^{\frac{1}{2}}$. Since $\phi$ is approximately half the *i*-factor (as defined above) in dilute solutions, Figs. 3 and 4 are similar in form.

*Comparison with Debye–Hückel theory.* For a uni-univalent electrolyte, the ionic strength in dilute solution is given by $I \sim m_2\rho$, where $\rho$ is the density of the pure solvent, and the Debye–Hückel osmotic equation [23] therefore becomes

$$\phi = 1 - \tfrac{1}{3}Am_2^{\frac{1}{2}}\sigma(x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where $$x = B\mathring{a}m_2^{\frac{1}{2}}; \quad \sigma(x) = \frac{3}{x^3}\left[(1 + x) - 2\ln(1 + x) - \frac{1}{1 + x}\right]$$

$$A = \frac{10^8Be^2}{2\varepsilon kT}; \quad 10^8B = \left(\frac{8\pi\rho Ne^2}{10^3\varepsilon kT}\right)^{3/2}$$

$\mathring{a}$ is the distance of closest approach of anion and cation in Ångström units, and $\varepsilon$ is the dielectric constant of the solvent. Taking the value of $\varepsilon$ at the melting point as 33·2, and that of $\rho$ as 2·683 g. cm.$^{-3}$, from Zhuravlev's density data,[24] we have

$$\phi = 1 - 1{\cdot}86m_2^{\frac{1}{2}}\sigma(0{\cdot}768\mathring{a}m_2^{\frac{1}{2}}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

for a uni-univalent electrolyte in antimony trichloride. The corresponding Debye–Hückel limiting law is obtained by putting $\mathring{a} = 0$, when $x = 0$ and $\sigma(x) = 1$ (as can be shown by expanding the $\sigma$-function into an infinite series):

$$\phi = 1 - 1{\cdot}86m_2^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

[20] Jander and Mesech, *Z. phys. Chem.*, 1939, **183**, *A*, 277.
[21] Bayles, Evans, and Jones, *J.*, 1955, 206.
[22] Gutmann, *Monatsh.*, 1954, **85**, 491.
[23] Robinson and Stokes, "Electrolyte Solutions," Butterworths, London, 1955, p. 233.
[24] Zhuravlev, *J. Phys. Chem., U.S.S.R.*, 1939, **13**, 684.

XUM

However, Fig. 4 shows that eqn. (8) is inadequate, because it predicts an osmotic coefficient which is always a decreasing function of concentration, whereas this is not so with triphenylmethyl and tetramethylammonium chlorides. The behaviour of non-associated electrolytes in water is similar, and to fit the results it is customary to add an empirical linear term, which has been interpreted [25] as mainly a correction for ion solvation. In our case, we can write

$$\phi = 1 - 1{\cdot}86m_2^{\frac{1}{2}}\sigma(0{\cdot}768\mathring{a}m_2^{\frac{1}{2}}) + bm_2 \quad . \quad . \quad . \quad . \quad . \quad (10)$$

where $b$ is a constant. Fig. 4 shows the values of $\mathring{a}$ and $b$ which give reasonable agreement between the curves calculated from eqn. (10) and the experimental results. For cæsium and potassium chlorides, the theoretical curves actually correspond to eqn. (8) ($b = 0$), although a better fit is obtained with negative values of $b$. Values of $\sigma(x)$ were obtained, by graphical interpolation, from tables [26] (in the range $x = 0$—1) and from further values ($x > 1$) calculated from the definition above.

To obtain theoretical values of $\mathring{a}$ for comparison with our results, we will assume that only the chloride ion is chemically solvated, and that it forms the anion $[SbCl_4]^-$, by analogy with Gutmann's suggestion [27] that the solvates $Me_4NCl,AsCl_3$ and $KCl,AsCl_3$ contain the anion $[AsCl_4]^-$. (We have not yet, however, succeeded in isolating similar compounds from antimony trichloride solutions.) Then $\mathring{a} = r^+ + r^-$ where $r^+$ is the radius of the cation, and $r^-$ is that of the $[SbCl_4]^-$ ion. Since the Sb–Cl bond length [28] is 2·4 Å, and the ionic radius of chlorine [29] is 1·8 Å, $r^- \sim 4{\cdot}2$ Å. The corresponding theoretical values of $\mathring{a}$ are compared with the experimental values in Table 2.

TABLE 2.

| Electrolyte | $r^+$ (Å) | $r^-$ (Å) | $\mathring{a}$ (Å) theor. | $\mathring{a}$ (Å) exp. |
|---|---|---|---|---|
| KCl | 1·3 [a] | 4·2 | 5·5 | 2·1 |
| CsCl | 1·7 [a] | ,, | 5·9 | 4·5 |
| $Me_4NCl$ | 3·5 [b] | ,, | 7·7 | 13 |
| $Ph_3CCl$ | *ca.* 5 [c] | ,, | between 7 and 9 | 15 |
| | (half-thickness *ca.* 2·5) | | | |

[a] Ref. 29. [b] Ref. 23, p. 119. [c] Hughes, Ingold, *et al.*, *J.*, 1957, 1276.

The triphenylmethyl cation is non-spherical, and hence only the upper and lower limits of $\mathring{a}_{theor}$ can be calculated.

For potassium and cæsium chlorides, the experimental $\mathring{a}$ parameters have obviously been forced to include the effects of association (Fig. 3) and have no geometrical significance, the apparent value for potassium chloride being too small even for completely unsolvated ions ($\mathring{a}_{theor} = 3{\cdot}1$). The Bjerrum critical distance for a uni-univalent electrolyte in antimony trichloride at its melting-point $T_0$ is

$$q = e^2/2\varepsilon kT_0 = 7{\cdot}3 \text{ Å}$$

Since the theoretical $\mathring{a}$ values for cæsium and potassium chlorides are less than this, ion-pair formation would be expected. It would also be expected for the chlorides of thallium ($r^+ = 1{\cdot}4$ Å), ammonium, and rubidium (both 1·5 Å); Fig. 1, indeed, shows that the limiting slopes of equivalent conductivity, $\Lambda$, against $C^{\frac{1}{2}}$ for $NH_4Cl$ and TlCl are considerably greater than the theoretical values, which would suggest incomplete dissociation; for RbCl, however, the discrepancy is quite small.

For the strong electrolytes, tetramethylammonium chloride and triphenylmethyl chloride, on the other hand, the observed distances of closest approach exceed not only the

[25] Gillespie and Oubridge, *J.*, 1956, 80.
[26] Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, 1950, p. 597.
[27] Gutmann, *Z. anorg. Chem.*, 1951, **266**, 331.
[28] Lindqvist and Niggli, *J. Inorg. Nuclear Chem.*, 1956, **2**, 345.
[29] Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, 1945.

critical distance, as expected, but also the theoretical values. In aqueous [30] and in sulphuric acid [25] solutions, the differences between the observed and crystallographic values of $\mathring{a}$ for non-associated electrolytes have been interpreted quantitatively in terms of solvation shells around the ions. In antimony trichloride solutions, one complete solvation shell around the $Ph_3C^+$ or $Me_4N^+$ cation would increase $\mathring{a}_{theor}$ (Table 2) to the observed order of magnitude, the molecular diameter of the solvent being about 6 Å. It is possible to estimate [25] a " solvation number " from the value of the parameter $b$, but the theoretical basis of such calculations is doubtful.

It is hoped to publish further results, concerning organic solutes which undergo reaction after initial ionisation.

We are indebted to Mr. D. A. Swann for some of the preparative work.

CHEMISTRY DEPARTMENT, ROYAL MILITARY COLLEGE OF SCIENCE,
SHRIVENHAM, WILTS. [*Received, August 28th*, 1957.]

[30] Stokes and Robinson, *J. Amer. Chem. Soc.*, 1948, **70**, 1870.

---

## 146. *Reactions of Tin*(IV) *Halides with Ammonia Derivatives. Part I. The Reaction of Tin*(IV) *Chloride with Liquid Ammonia.*

E. BANNISTER and G. W. A. FOWLES.

The reaction of tin(IV) chloride with liquid ammonia gives mainly ammonium chloride and the ammonobasic tin(IV) chloride, $SnCl(NH_2)_3$; the latter can be prepared pure by thorough washing with liquid ammonia. A tensimetric study of the reaction shows that ammonium chloride and $SnCl(NH_2)_3$ are formed at $-63°$, but that at higher temperatures ($-45°$ and $-36°$) there is further reaction with the formation of a complex tin species, $[NH_4]_2[SnCl_3(NH_2)_3]$. The progressive thermal decomposition of all the initial products shows the existence of various intermediate mixtures, with the eventual production of a readily sublimable diammine of tin(IV) chloride, $(SnCl_4,2NH_3)$.

The mechanism of the various reactions is discussed.

STUDIES of the ammonolysis of the chlorides of the Group IVB elements show that although carbon tetrachloride does not react with liquid ammonia at its boiling point,[1] silicon(IV) chloride [2] and germanium(IV) chloride [3] are completely ammonolysed to the amide and imide respectively, while tin(IV) chloride forms an ammonobasic chloride. No evidence has been presented for the ammonolysis of lead(IV) chloride.

Early investigators [4] showed that tin(IV) chloride reacted with gaseous ammonia at room temperature to give a white compound $SnCl_4,4NH_3$, which gave a sublimate $SnCl_4,2NH_3$ when heated. Both substances were simply formulated as addition compounds. Schwarz and Jeanmaire [5] considered that the reaction of tin(IV) chloride with ammonia might give a mixture of ammonium chloride and an ammonobasic tin(IV) chloride, and proved this by washing their product with liquid ammonia to extract the soluble ammonium chloride, leaving the insoluble ammonobasic tin(IV) chloride $SnCl(NH_2)_3$. Our investigations confirm Schwarz and Jeanmaire's observations except that we found it unnecessary to heat the product to 100° between washes to remove ammonium chloride completely.

[1] Watt and Hahn, *J. Amer. Chem. Soc.*, 1955, **77**, 312.
[2] Vigoureux and Hugot, *Compt. rend.*, 1903, **135**, 1670.
[3] Thomas and Pugh, *J.*, 1931, 60.
[4] Mellor, " A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green & Co., London, Vol. VII, 1927, p. 445.
[5] Schwarz and Jeanmaire, *Ber.*, 1932, **65**, 1443.

XUM

We consider that the ammonolysis proceeds in a number of stages:

$$SnCl_4 + 2NH_3 \rightleftharpoons SnCl_3NH_2 + NH_4Cl \quad \text{(i)}$$
$$SnCl_3NH_2 + 2NH_3 \rightleftharpoons SnCl_2(NH_2)_2 + NH_4Cl \quad \text{(ii)}$$
$$SnCl_2(NH_2)_2 + 2NH_3 \rightleftharpoons SnCl(NH_2)_3 + NH_4Cl \quad \text{(iii)}$$
$$SnCl(NH_2)_3 + 2NH_3 \rightleftharpoons Sn(NH_2)_4 + NH_4Cl \quad \text{(iv)}$$

and that the removal of the ammonium chloride by washing pulls over the equilibria until $SnCl(NH_2)_3$ is left as the main product. Each stage will follow the usual solvolysis pattern of the initial co-ordination of ammonia molecules followed by the elimination of hydrogen chloride under the influence of the solvent ammonia molecules:

$$SnCl_4 + 2NH_3 \longrightarrow [SnCl_4,2NH_3] \longrightarrow SnCl_3NH_2 + NH_4Cl$$

With the replacement of chlorine atoms by amino-groups the tin will become a much poorer acceptor so that the reaction will not go completely to the tin(IV) amide.

Now if there is any ammonium chloride present it will form a triammoniate with a distinctive dissociation pressure,[6] and a tensimetric study of the $SnCl(NH_2)_3$–$NH_3$ system will show us if ammonium chloride is present; each three moles of ammonia present at the known dissociation pressure of the ammonium chloride triammoniate correspond to the presence of one mole of ammonium chloride. From Fig. 1(*a*) we see that there is no appropriate univariant portion, so that no ammonium chloride can be present.

The tensimetric study of the tin(IV) chloride–ammonia reaction at −63° [cf. Fig. 1(*c*)] shows that 2·6 mol. of ammonium chloride are produced in the initial equilibrium reaction, so that the product is largely $SnCl(NH_2)_3$ together with a little $SnCl_2(NH_2)_2$. This agrees with the washing experiments, where removal of ammonium chloride left $SnCl(NH_2)_3$.

At reaction temperatures of −36° and −45°, however [cf. Fig. 1(*b*)], only slightly more than 1 mol. of ammonium chloride can be detected. Now an increase in temperature should tend to increase the amount of ammonolysis and produce more ammonium chloride, so it appears that some of the ammonium chloride is not being detected tensimetrically. A reasonable interpretation would be that some ammonium chloride interacts with the ammonobasic tin chloride to form one single phase; this ammonium chloride would then remain undetected since it could not form its characteristic triammoniate. One obvious explanation is the formation of an anionic tin(IV) complex between the ammonobasic tin chloride and ammonium chloride:

$$SnCl(NH_2)_3 + 2NH_4Cl \longrightarrow [NH_4]_2[SnCl_3(NH_2)_3]$$

Some evidence for this behaviour is afforded by the washing runs, where a considerable amount of tin is found together with the ammonium chloride in the filtrate. In the washing experiments, we would expect some of the ammonobasic tin chloride to form a complex and be carried over with the ammonium chloride; all the tin would not be in the form of a complex because the ammonium chloride concentration is relatively low—a large excess of liquid ammonia being present. This type of complex-forming action is quite common, and experiments with the insoluble ammonobasic chlorides of titanium(IV), vanadium(IV), and molybdenum(V)[7] have shown that solution is readily affected by the addition of ammonium salts.

This complex-formation is evidently irreversible, because after the excess of ammonia has been removed at −36°, the product can be cooled to −63° in the presence of further ammonia, and a new tensimetric study again shows only 1 mol. of ammonium chloride to be present. On the other hand, in the similar repetition of a −63° run at −36°, the amount of ammonium chloride found changes from almost 3 mol. to the 1 mol. usually found at −36°.

Therefore we must account for complex-formation's occurring only at −45° and −36°

[6] Fowles and Pollard, *J.*, 1952, 4938.
[7] Fowles, unpublished observations.

and not at −63°. A probable explanation is that at −63° the solubility of ammonium chloride (and the ammonobasic tin chloride) is so low that complex-formation would be very slight, whereas at the higher temperatures the much greater solubility of ammonium chloride and correspondingly acidic solution produces complex-formation.

There should, on our simple theory, be 3 mol. of ammonium chloride detectable at −63° and one at −36°, and the slightly greater amount of ammonium chloride at −36° must be accounted for either in terms of a somewhat greater ammonolysis with the increased temperature or incomplete complex-formation; we should, for instance, expect complex-formation to be incomplete if the ammonobasic tin chloride was polymeric (caused by elimination of hydrogen chloride between neighbouring molecules).

FIG. 1.

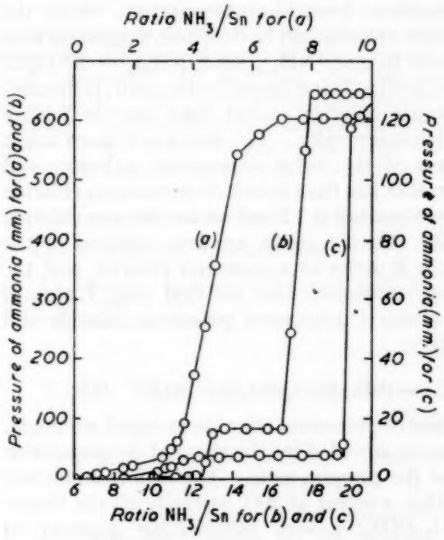
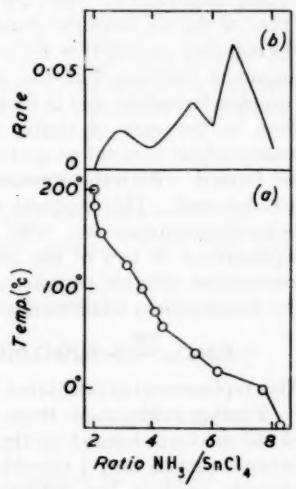

Ratio NH3/Sn for (a)
0 2 4 6 8 10
Pressure of ammonia (mm) for (a) and (b)
600 500 400 300 200 100 0
Pressure of ammonia (mm.) for (c)
120 100 80 60 40 20 0
(a)
(b)
(c)
6 8 10 12 14 16 18 20
Ratio NH3/Sn for (b) and (c)

FIG. 2.




The thermal decomposition between 0° and 200° of the products formed at all three temperatures gives very similar results (Fig. 2), which strongly suggest intermediate compounds of some stability. Since the liberated ammonia diffuses only slowly through the solid, successive decompositions will tend to overlap, and the decomposition curves show slope changes rather than vertical portions at the more stable intermediate compositions.

These intermediate compounds have the overall formula $SnCl_4,xNH_3$, with $x = 6$, 4, and 2. Assuming that the product of the tin(IV) chloride–ammonia reaction at −63° contains a mixture of ammonium chloride and an ammonobasic tin chloride, we explain the stepwise decomposition of the ammonolysis products as follows:

$SnCl(NH_2)_3 + 3NH_4Cl$ corresponding to $SnCl_4,6NH_3$

↓

$SnCl_2(NH_2)_2 + 2NH_4Cl$ (+ $2NH_3$ ↑) corresponding to $SnCl_4,4NH_3$

↓

$SnCl_3(NH_2) + NH_4Cl$ (+ $2NH_3$ ↑) corresponding to $SnCl_4,2NH_3$

↓

$SnCl_4 + 2NH_3$ which react immediately outside the hot zone to give $SnCl_4,2NH_3$

We consider that complex anionic tin species have been formed in the reactions at −45° and −36°, and the subsequent thermal decompositions will follow the scheme:

$$[NH_4]_2[SnCl_3(NH_2)_3] + NH_4Cl \text{ corresponding to } SnCl_4,6NH_3$$
$$\downarrow$$
$$[NH_4][SnCl_3(NH_2)_3] + NH_4Cl\ (+ 2NH_3\uparrow) \text{ corresponding to } SnCl_4,4NH_3$$
$$\downarrow$$
$$SnCl_3(NH_2) + NH_4Cl\ (+ 2NH_3\uparrow) \text{ corresponding to } SnCl_4,2NH_3$$

This again reacts to form the diammine of tin(IV) chloride.

In these thermal decompositions, the tin–nitrogen bonds break, in contrast to the tin–chlorine bond rupture found in the base-catalysed reactions in liquid ammonia.

To provide further evidence about the nature of the anionic tin complexes, we studied the ammonolysis of diammonium and dipotassium hexachlorostannate(IV). With the diammonium salt at −36°, 2·8 mol. of ammonium chloride can be detected, suggesting that three of the six chlorine atoms can be replaced to give $[NH_4]_2[SnCl_3(NH_2)_3] + 3NH_4Cl$; the complex anion is thus the same as that postulated as being formed in the tin(IV) chloride–ammonia reaction, but the liberated ammonium chloride cannot take part in further complex-formation and is therefore detected tensimetrically. The solution is more acidic than in the case of tin(IV) chloride, because of the extra ammonium chloride, and ammonolysis does not go quite as far, so that rather less than 3 mol. of ammonium chloride are formed. With the dipotassium hexachlorostannate(IV) 1·2 mol. of ammonium chloride are detected. This suggests that three of the chlorine atoms are first replaced in the hexachlorostannate ion, with the formation of 3 moles of ammonium chloride and the replacement of two of the potassium ions by ammonium ions (so that only 1 mol. of ammonium chloride remains to be detected) giving a mixture of potassium chloride and the diammonium triamminotrichlorostannate(IV):

$$K_2SnCl_6 \xrightarrow{NH_3} K_2[SnCl_3(NH_2)_3] + 3NH_4Cl \longrightarrow [NH_4]_2[SnCl_3(NH_2)_3] + NH_4Cl + 2KCl$$

This replacement is facilitated by the insolubility of potassium chloride in liquid ammonia.

Further evidence for these reaction schemes is provided by the thermal decomposition of the mixtures formed by the ammonolysis of the complex salts. The diammonium salt behaves just as tin(IV) chloride itself, except that whereas at 200° virtually all the tin(IV) chloride product has sublimed, giving $SnCl_4,2NH_3$, a very considerable quantity of ammonium chloride still remains behind from the complex salt product. Thus although the sublimate of diamminotin(IV) chloride forms readily, the massive ammonium chloride sublimes only very slowly at 200°. With the dipotassium product, a similar thermal decomposition is observed, but the substantial residue remaining at 200° is now potassium chloride.

## Experimental

*Materials.*—Tin(IV) chloride (Messrs. British Drug Houses) was distilled *in vacuo* into suitable ampoules.[8] Ammonia (from Imperial Chemical Industries Limited) was dried (Na) and condensed into the vacuum line. The ammonium and potassium hexachlorostannate(IV) were prepared by the reaction of tin(IV) chloride (1 mol.) and the appropriate chloride (2 mol.) in dilute hydrochloric acid [Found: Cl, 57·4; N, 7·6. Calc. for $(NH_4)_2SnCl_6$: Cl, 57·9; N, 7·6. Found: Sn, 29·0; Cl, 52·0. Calc. for $K_2SnCl_6$: Sn, 29·0; Cl, 51·9%].

*Analysis.*—Complete analyses were normally carried out, but whenever the product firmly adhered to the reaction vessel it was hydrolysed with dilute sulphuric *in situ*, so that subsequent analysis gave only the Sn : Cl : N ratio.

Nitrogen was determined as ammonia by distillation from an alkaline solution into boric acid solution,[9] followed by titration with standard hydrochloric acid solution (B.D.H. 4·5 indicator).

[8] Fowles and Pleass, *J. Chem. Educ.*, 1956, **33**, 640.

[9] "Standard Methods of Analysis of Iron, Steel and Ferroalloys," The United Steel Companies, Ltd., Sheffield, 1951, 4th edn., p. 55.

Tin was determined as the oxide [10] by ignition of the precipitated hydroxide. Chlorine was determined potentiometrically as chloride by titration with standard silver nitrate solution, by use of lead–lead sulphate and silver–silver chloride half-cells.

*Reactions and Tensimetric Studies.*—All reactions were carried out in the usual type of closed vacuum system.[6, 11]

The voluminous white solid produced by the direct reaction of tin(IV) chloride and ammonia at −33·5° was washed extensively (15 × 50 ml.) with liquid ammonia to remove ammonium chloride; the solid remaining was pumped for several hours at room temperature before analysis [Found: Sn, 57·9; Cl, 18·3; N, 20·1%; Sn : Cl : N, 1 : 1·06 : 2·94. $SnCl(NH_2)_3$ requires Sn, 58·7; Cl, 17·5; N, 20·8%].

This *product* was allowed to come into contact with excess of ammonia at −36°, and a tensimetric study was made of the $SnCl(NH_2)_3$–$NH_3$ system [Fig. 1(*a*)].

The $SnCl_4$–$NH_3$ system was studied tensimetrically at −36°, −45°, and −63°, and the results of the −36° and −63° investigations are shown in Figs. 1(*b*) and 1(*c*) respectively.

*Thermal Decompositions.*—These were carried out on the products remaining after removal of excess of ammonia at the reaction temperature, by heating the sample *in vacuo* for 2 hr. at successive intervals of about 20°, the ammonia liberated at each temperature being condensed and measured.[6] In this way the following compounds were thermally decomposed: $SnCl_4,8NH_3$, $(NH_4)_2SnCl_6,8NH_3$, and $K_2SnCl_6,8NH_3$. (Only the overall compositions are quoted.) The results of these decompositions are illustrated in Fig. 2 (rate in moles of ammonia deg.$^{-1}$ hr.$^{-1}$). The white sublimate which was formed above 120° was analysed in each case, Sn : Cl : N being 1·0 : 3·88 : 2·10, 1·0 : 4·10 : 2·10, and 1·0 : 3·99 : 2·06 respectively.

We thank the International Tin Research Council for a maintenance grant (to E. B.).

THE UNIVERSITY, SOUTHAMPTON. [*Received, September 10th*, 1957.]

[10] Hillebrand, Lundell, Bright, and Hoffman, "Applied Inorganic Analysis," Wiley, New York, 1953, 2nd edn., p. 287.
[11] Fowles and Pleass, *J.*, 1957, 1674.

---

## 147. *The Chemistry of Bacteria. Part VII.* The Structure of Violacein.*

By J. A. BALLANTINE, C. B. BARRETT, R. J. S. BEER, STEPHEN EARDLEY, ALEXANDER ROBERTSON, B. L. SHAW, and T. H. SIMPSON.

Examination of a methylation product of violacein suggests two possible molecular formulæ for the pigment, namely $C_{21}H_{15}O_3N_3$ and $C_{20}H_{13}O_3N_3$. The latter formula offers the more satisfactory explanation of the behaviour of violacein with alkaline reagents and leads to structure (IV). Other structures, based on the $C_{21}$ formula, are briefly discussed.

VIOLACEIN, the violet pigment of *Chromobacterium violaceum*, is also produced by a marine bacterium, isolated from the skin slime of iced North Sea Cod and provisionally designated *Chromobacterium*, Strain B.C.1. This organism differs from *Chromobacterium violaceum* morphologically, in its behaviour towards antibiotics, and in being chitinivorous.† Recognition of the identity of the pigments from the two sources has been facilitated by the discovery that violacein can be methylated with methyl sulphate and potassium carbonate, giving a blue highly crystalline (and easily crystallised) compound, $C_{23}H_{18}O_2N_3{\cdot}OMe$ or $C_{22}H_{16}O_2N_3{\cdot}OMe$. The formation of this derivative must involve the introduction of at least three methyl groups, since on degradation with alkali and zinc dust it gave the trimethyl derivative (I; R = Me) of the $C_{20}$ acid, γ-(5-hydroxy-3-indolyl)-α-(3-oxindolyl)-γ-oxobutyric acid, previously reported,[1,2] and on being pyrolysed furnished

* Part VI, *J.*, 1957, 4810.
† We are grateful to Dr. J. H. Shewan of the Torry Research Station, Aberdeen, for supplying this information.

[1] Ballantine, Barrett, Beer, Boggiano, Clarke, Eardley, Jennings, and Robertson, *J.*, 1957, 2222.
[2] Barrett, Beer, Dodd, and Robertson, *J.*, 1957, 4810.

XUM

5-methoxy-1-methylindole and 1-methyloxindole. On the basis of this evidence there are two possible molecular formulæ for the parent pigment, namely, $C_{21}H_{15}O_3N_3$ and $C_{20}H_{13}O_3N_3$, neither of which is inconsistent with the rather erratic analytical data obtained with violacein samples. At present these data are of uncertain value because the insolubility of the pigment and its tendency to retain solvents, *e.g.*, pyridine, make absolute purification difficult. From the results so far obtained in the degradation of violacein it appears clear that a $C_{20}$ or $C_{21}$ empirical formula is to be preferred to the formula, $C_{42}H_{28}O_7N_6$, suggested by Wrede and Swane.[3] By the magnesium iodide method partial demethylation of the methylated pigment gave a product which, although it could not be satisfactorily purified, afforded crystalline acetyl and benzoyl derivatives. The analyses of these derivatives, however, do not serve to distinguish between the $C_{20}$ and the $C_{21}$ formula.

An important feature in the chemistry of violacein is the behaviour of the compound with alkaline reagents, a preliminary account of which has been given by Wrede and Swane.[3] According to these authors violacein dissolves in aqueous sodium hydroxide, giving an intense emerald-green solution which soon becomes red, a change much accelerated on warming. From this solution a red solid (A) is precipitated by saturation with carbon dioxide, and on acidification with mineral acid the filtrate gives an unstable yellow solid (B) which darkens rapidly. Wrede and Swane considered solids (A) and (B) to be very closely related to violacein, claiming that both regenerate violacein with hot pyridine and give the acetyl derivative of the pigment on acetylation.

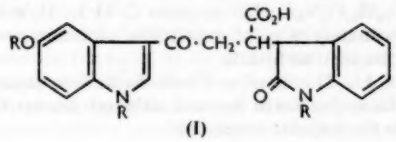
We have confirmed the production of compounds (A) and (B) from violacein but, whereas an examination of (A) supports Wrede and Swane's view that it is a modified form of violacein, a study of the yellow solid (B) indicates that it is a degradation product. Thus, on acetylation, the compound (B) gives a product which superficially resembles the acetyl derivative of violacein but has a different infrared absorption and a lower nitrogen content. This acetate was found to be identical with the " red lactone " [1] derived from the $C_{20}$ acid and therefore has structure (II; R = Ac). As the substance (B) is *not* precipitated from the alkaline reaction mixture with carbon dioxide it may reasonably be regarded as a carboxylic acid. The conditions under which (B) is formed differ from those which give rise to the $C_{20}$ acid only in the absence of zinc, a reducing agent. It seems probable that compound (B) is an oxidised form of the $C_{20}$ acid, *viz.*, (III; R = H), a structure which accounts for the colour of (B) and for its instability, since compounds of this type are very easily converted into unsaturated lactones.[2] The darkening of compound (B) may be attributed to the formation of the lactone (II; R = H). On this account it has not been possible to purify compound (B), and the almost black solid (C), presumably (II; R = H) derived from it by the action of dilute mineral acid, has yielded only minute amounts of crystalline material. Nevertheless, a number of transformations have been carried out which support the above views. Thus, as expected, reduction of compound (B) with zinc and alkali affords the $C_{20}$ acid. On acetylation, material (C) is converted into the " red lactone " (II; R = Ac) and on methylation into the " magenta lactone " [1] (II; R = Me) which was also obtained from the methyl derivative of violacein by degradation with alkali and treatment of the resulting unstable yellow product, presumably (III; R = Me), with dilute aqueous acid.

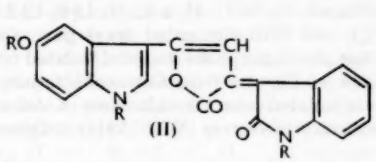
The formation of the yellow products (III; R = H and Me) by the relatively mild treatment of violacein and its methyl derivative respectively with alkali is explained on the assumption that violacein has the molecular formula, $C_{20}H_{13}O_3N_3$. The pigment must then have structure (IV) which would be expected to be alkali-sensitive. This structure also readily accounts for the formation of the $C_{20}$ acid and ammonia by reductive hydrolytic fission of violacein.

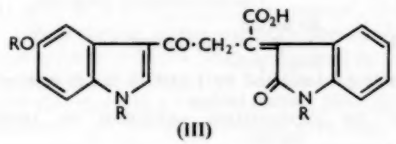
On the other hand structures based on a $C_{21}H_{15}O_3N_3$ formula, *e.g.*, (V) and (VI), do not appear to offer a satisfactory explanation of the degradation reactions discussed above.

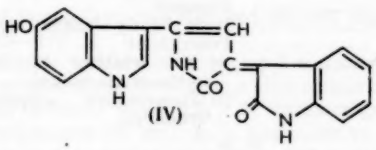
[3] Wrede and Swane, *Arch. exp. Pathol. Pharmakol.*, 1937, **186**, 532.

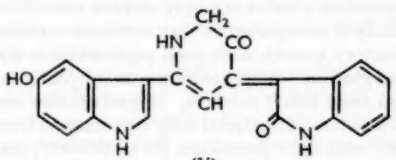
Whilst a compound of formula (V) might conceivably yield a 3-acylindole on alkaline hydrolysis, the generation of the carboxyl group in compounds (III; R = H and Me) and in the $C_{20}$ acid presents difficulties. Stoicheiometric considerations indicate that the carbon atom which is lost would separate as methanol but attempts to isolate this unit

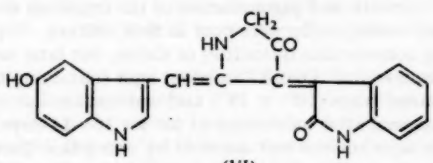

(I)


(II)


(III)


(IV)


(V)


(VI)

from the hydrolysate have so far been unsuccessful. The structure (VI), which was originally proposed to account for the formation of a supposed indolylpyrrylmethene [4] from acetylviolacein by the action of hydriodic acid, does not explain the formation of either the carbonyl or the carboxyl group in the alkaline degradation products, and structures of the trisubstituted methene type referred to in Part III [4] are similarly excluded. Clearly structure (IV), which is otherwise acceptable, could not give rise to an indolylpyrrylmethene, and it therefore seems necessary to re-examine this hydriodic acid degradation product.

In connection with the isolation of violacein from *Chromobacterium*, B.C.1. it may be noted that one of us (A. R.) in collaboration with Dr. T. S. Subramaniam (lately of this Department) isolated in 1939 a pigment from *Chromobacterium janthinum* which appeared to be closely related to, if not identical with, violacein (the compounds had identical ultraviolet absorption spectra), a result in agreement with the view that biologically *Chr. janthinum* is very similar to *Chr. violaceum*.[5]

## Experimental

(With B. G. Boggiano, K. Clarke, and T. S. Subramaniam.) *Violacein from* Chromobacterium violaceum.—The organism grows and pigments well at room temperature on a solid medium containing agar (1·8—2·0%), glycerol (2%), and proteose peptone (Difco; 1%) made up in tap-water. For large-scale cultivation, this medium was supported on enamel trays (20″ × 15″); inoculation was effected with sterile cotton-wool plugs from vigorous cultures growing on a similar medium contained in glass casseroles. After 12—14 days the bacterial mass was scraped from the surface of the medium, spread on filter-paper, and allowed to dry. The resulting brittle, almost black product was milled and then extracted (Soxhlet) with acetone, the pigment separating, usually highly crystalline. Impurities were removed from the crystalline solid by washing it with water and repeatedly extracting it with hot chloroform.

[4] Beer, Jennings, and Robertson, *J.*, 1954, 2679.
[5] Topley and Wilson, "Principles of Bacteriology and Immunity," Arnold, London, 1943, p. 497.

Purified for analysis by repetition of the acetone-extraction process, violacein formed almost black prisms with a green sheen (Found: C, 69·3, 69·0, 69·5; H, 3·8, 4·1, 4·3; N, 11·7, 11·1; O, 15·0. Calc. for $C_{21}H_{15}O_3N_3$: C, 70·6; H, 4·2; N, 11·8; O, 13·4. Calc. for $C_{20}H_{13}O_3N_3$: C, 70·0; H, 3·8; N, 12·2; O, 14·0. Calc. for $C_{20}H_{13}O_3N_3,\frac{1}{3}C_3H_6O$: C, 69·3; H, 4·3; N, 11·3; O, 15·1%). Repeated crystallisation from aqueous pyridine gave the *pyridine complex* in violet needles (Found: C, 70·7; H, 4·3; N, 13·0, 12·2. $C_{20}H_{13}O_3N_3,C_5H_5N$ requires C, 71·1; H, 4·3; N, 13·3%). 80 Well-pigmented trays gave approximately 8 g. of crystalline violacein and 3·5 g. of less pure amorphous material isolated from the acetone filtrate.

*Isolation of Pigment from* Chromobacterium B.C.1.—This marine *Chromobacterium*, strain B.C.1., was isolated from the skin slime of iced cod from the North Sea and although similar to *Chromobacterium violaceum* (NCTC 7917) it differed in the respects tabulated.

| Test | *Chromobacterium* B.C.1 | *Chromobacterium violaceum* |
|---|---|---|
| Chitin | Digested | No action |
| Milk | Made slightly alkaline; clotted | Completely peptonised |
| Flagella | Peritrichous | Single polar |
| Antibiotics | (*a*) Not inhibited by 10 m.c.g. erythromycin tablets | Inhibited by 1 and 10 m.c.g. erythromycin tablets |
| | (*b*) Pigmentation suppressed by terramycin | Pigmentation unaffected by terramycin |

Growth and pigmentation of the organism were good only under strongly aerobic conditions and consequently were poor in fluid culture. Originally it was grown on nutrient agar containing considerable quantities of chitin, but later satisfactory growth with good pigmentation was obtained on " Oxoid " nutrient agar containing 1% of glucose. This medium was supported on enamel trays (16″ × 13″) and was surface-inoculated from liquid cultures. Pigmentation was maximal after incubation at 25° for 10—14 days. The mass of bacterial cells was scraped from the agar surface and defatted by extraction (Soxhlet) with light petroleum (b. p. 60—80°) and the pigment then extracted with hot acetone. Evaporation of the extract left the compound as a blue-black microcrystalline powder which was purified by repeatedly washing it with hot water and hot light petroleum until the washings were colourless (yield, *ca.* 80 mg. per tray). This pigment had the same properties as violacein and by a comparison of visible, ultraviolet, and infrared absorption spectra the compound was shown to be identical with the pigment from *Chromobacterium violaceum*.

*Methylation of Violacein.*—(*a*) A mixture of violacein (5·0 g. from *Chromobacterium*, Strain B.C.1.), methyl sulphate (10 ml.), an excess of potassium carbonate, and acetone (500 ml.) was heated under reflux for 8 hr., then filtered (wash with acetone), and the combined filtrate and washings were concentrated in a vacuum to a small volume. The residue was agitated overnight with aqueous sodium hydrogen carbonate to decompose unchanged methyl sulphate, and the residual blue solid isolated, dissolved in benzene, and purified by chromatography on aluminium oxide. Evaporation of the benzene eluate left the *methylated pigment* which crystallised from alcohol in blue needles (4 g.), m. p. 218° (Found: C, 72·1; H, 5·3; N, 10·4; OMe, 8·0%; *M*, 380. $C_{23}H_{18}O_2N_3$·OMe requires C, 72·2; H, 5·3; N, 10·5; OMe, 7·8%; *M*, 399. $C_{22}H_{16}O_2N_3$·OMe requires C, 71·7; H, 5·0; N, 10·9; OMe, 8·1%; *M*, 385).

(*b*) Application of the same methylation procedure to violacein (200 mg.) from *Chromobacterium violacein* followed by recrystallisation of the product from benzene gave blue needles (150 mg.), m. p. 127°, containing solvent of crystallisation; the unsolvated *compound* separated from ethyl acetate in blue needles, m. p. 220°, $\lambda_{max.}$ (in EtOH) 270, 376, 580 mμ (log ε 4·31, 3·88, 4·29), $\lambda_{min.}$ 243, 333, 440 mμ (log ε 4·26, 3·65, 3·34) (Found: C, 71·8, 72·0; H, 5·1, 5·2; N, 10·4, 10·7; OMe, 8·2, 7·8%; *M*, 405), and was shown by mixed m. p. determination and by comparison of visible, ultraviolet, and infrared absorption spectra to be identical with the methylated pigment, m. p. 218°, from (*a*). Methylated violacein is readily soluble in chloroform or benzene, moderately soluble in alcohol, and insoluble in aqueous sodium hydroxide. It did not form an oxime and was recovered in good yield after being heated with acetic anhydride and sodium acetate under reflux for ½ hr.

A mixture of methylated violacein (100 mg.), in alcohol (15 ml.), 2N-aqueous sodium hydroxide (15 ml.), and zinc dust (200 mg.) was heated under reflux for 1 hr., filtered, and acidified, giving the trimethyl derivative [1] of the $C_{20}$ acid (60 mg.), m. p. 260°, which crystallised from acetone in prisms, m. p. and mixed m. p. 267°.

*Partial Demethylation of Methylated Violacein.*—A solution of methylated violacein (55 mg.)

in benzene was added to ethereal magnesium iodide (freshly prepared from 500 mg. of iodine and an excess of magnesium), and the mixture heated under reflux for ½ hr. After evaporation of the solvents in a vacuum the residual green-red complex was heated in a vacuum at 150° for 1 hr. and the residue decomposed with dilute acetic acid. The resulting blue solid did not crystallise satisfactorily and was converted by acetic anhydride–pyridine into the *acetyl derivative* which after purification by chromatography on aluminium oxide from chloroform–benzene crystallised from alcohol and then light petroleum (b. p. 100—120°) in dark purple needles (25 mg.), m. p. 219—221° (Found: C, 70·3; H, 5·0; N, 9·8. $C_{21}H_{12}O_3N_3Me_2$·COMe requires C, 70·2; H, 5·0; N, 9·8. $C_{20}H_{10}O_3N_3Me_2$·COMe requires C, 69·7; H, 4·6; N, 10·2%). Prepared by the benzoyl chloride–pyridine method, the *benzoyl derivative* of the partially demethylated product separated from acetone–light petroleum (b. p. 60—80°) in dense, dark blue needles, m. p. 241—243° (Found: C, 73·6; H, 4·7; N, 8·7. $C_{30}H_{23}O_4N_3$ requires C, 73·6; H, 4·7; N, 8·6. $C_{29}H_{21}O_4N_3$ requires C, 73·3; H, 4·5; N, 8·8%).

Methylation of the partially demethylated material by the standard method regenerated methylated violacein, m. p. and mixed m. p. 215—218°.

*Pyrolysis of Methylated Violacein.*—An intimate mixture of methylated violacein (1·5 g.) and zinc dust (15 g.) was heated to 300—310° under reduced pressure in a slow stream of carbon dioxide, and the oily distillate (180 mg.) thus obtained was purified by chromatography on aluminium oxide. From this 5-methoxy-1-methylindole (39 mg.), m. p. and mixed m. p. 104—105°, was eluted with ether–light petroleum (b. p. 40—60°), a trace of 5-methoxyindole with ether, and then 1-methyloxindole (109 mg.), m. p. and mixed m. p. 85—87°, with ether–chloroform (100 : 1).

*Degradation of Violacein with Alkali.*—Violacein (500 mg.) was heated with 0·1N-aqueous sodium hydroxide (70 ml.) in nitrogen under reflux for 35 min. The undissolved violacein (*ca.* 50 mg.) was removed by filtration and the solution then heated for a further 5 min., cooled, and saturated with carbon dioxide (by addition of " dry ice "). The precipitated " red solid " (A) (150 mg.) was collected and on acidification with 2N-hydrochloric acid the filtrate gave a bright yellow solid (B) (150 mg.) which was thoroughly washed with water (in contact with acid, this yellow solid rapidly became green and eventually almost black) and dried. Longer interaction of violacein with alkali gave relatively less " red solid " and more " yellow solid."

*Reactions of the Yellow Solid* (B).—When kept at room temperature the solution obtained by heating the yellow solid (B) (170 mg.) under reflux with acetic anhydride (15 ml.) and sodium acetate (200 mg.) for 10 min. slowly deposited a red crystalline product, m. p. *ca.* 280°, having an infrared absorption spectrum identical with that of the " red lactone " [1] derived from the $C_{20}$ acid. Treated with zinc dust and hot alkali, the yellow solid (B) was converted into the $C_{20}$ acid, m. p. and mixed m. p. *ca.* 245°, having the requisite infrared absorption spectrum.

With warm dilute hydrochloric acid the solid (B) was converted into an almost black solid (C) which was extracted (Soxhlet) with ethyl acetate and partially purified by chromatography from the same solvent on silica gel. The resulting dark amorphous product gave wine-red or purple solutions, differing from those given by violacein. A solution of the *substance* in acetic acid deposited a small quantity of very dark plates with a green sheen, m. p. *ca.* 330° (Found: N, 7·9. $C_{20}H_{12}O_4N_2$ requires N, 8·1%).

*Reactions of Solid* (*C*).—The partly purified solid (C) (200 mg.) was mixed intimately with potassium carbonate and heated under reflux with acetone (30 ml.) and methyl sulphate (1·0 ml.) for 17 hr. The filtered solution was concentrated, the sticky residue was triturated with water, and the crude product was isolated with benzene and chromatographed from this solvent on silica. Eluted with benzene containing a little ethyl acetate and then recrystallised from benzene, the product formed dark needles with a green reflux (50 mg.), m. p. 268°, identical with the " magenta lactone " [1] and having the requisite infrared absorption spectrum. Heated with acetic anhydride and sodium acetate, the solid (C) gave the " red lactone " [1] in dark red needles, m. p. and mixed m. p. 282°.

*Reactions of the Red Solid* (*A*).—On being heated with dilute aqueous sodium hydroxide under reflux for 1 hr., the red solid (A) (450 mg.) was partially converted into the yellow solid (B) (200 mg.) with some unchanged starting material (*ca.* 100 mg.). With methyl sulphate and potassium carbonate in boiling acetone, the red solid (A) (150 mg.) gave the methyl derivative of violacein (60 mg.), m. p. and mixed m. p. 220°; more methyl derivative (40 mg.) was obtained by further methylation of an acetone-insoluble salt-like by-product which had been digested with dilute aqueous acid.

XUM

*Degradation of Methylated Violacein with Alkali.*—The solution formed by heating the methyl derivative of violacein (500 mg.) with acetone (150 ml.) and N-aqueous sodium hydroxide (150 ml.) in nitrogen for 1 hr. was filtered, cooled, and acidified, giving a yellow solid. This mixture was warmed and the resulting dark solid (400 mg.) collected and dried. On purification by chromatography from benzene on silica and then by crystallisation from benzene this gave the " magenta lactone " [1] in dark needles with a green sheen (100 mg.), m. p. and mixed m. p. 266°, having the requisite infrared absorption spectrum (Found: C, 71·4; H, 4·8; N, 7·6. Calc. for $C_{23}H_{18}O_4N_2$: C, 71·5; H, 4·7; N, 7·3%).

UNIVERSITY OF LIVERPOOL.
TORRY RESEARCH STATION, ABERDEEN.

[*Received, July 30th*, 1957.]

---

## 148. *Infrared Absorption of* NMe *and* $NMe_2$ *Groups in Amines.*

By R. D. HILL and G. D. MEAKINS.

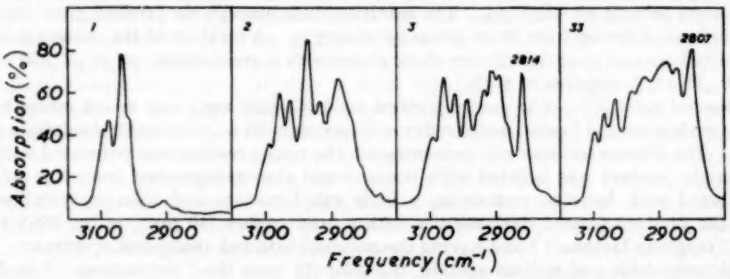
The following correlations have been established for the infrared spectra of amines. An NMe group attached to, or contained in, an aromatic system gives a characteristic band between 2820 and 2810 cm.$^{-1}$. When the group is in an aliphatic, or a non-aromatic heterocyclic, system the band occurs in the 2805—2780 cm.$^{-1}$. range.

The $NMe_2$ group directly attached to an aromatic system absorbs near 2800 cm.$^{-1}$, while an $NMe_2$ group not so attached has two specific bands, one between 2825 and 2810 cm.$^{-1}$, and the other between 2775 and 2765 cm.$^{-1}$.

RECENTLY [1] it was shown that the frequencies of the characteristic infrared absorption bands of the methyl group vary according to the nature (carbon or oxygen) of the atom to which the group is attached. This variation led to a method for detecting methoxyl groups in organic compounds by a specific band between 2832 and 2815 cm.$^{-1}$, arising from the symmetric CH stretching vibration of the $OCH_3$ unit.

The work has now been extended by examining the spectra of a series of amines containing NMe and $NMe_2$ groups (see Table). This topic has been briefly mentioned by Colthup.[2] With few data available the tentative (erroneous) conclusion reached was that the symmetric CH stretching frequency of the methyl group is increased when the group is attached to nitrogen.

*Absorption spectra of* 1, *aniline*; *and* 2, N-*ethyl*-; 3, N-*methyl*-; *and* 33, NN-*dimethyl-aniline*.



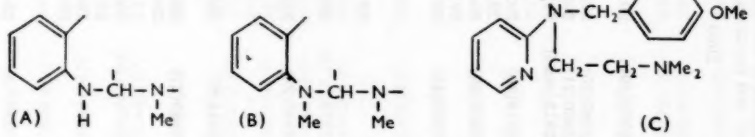

Some amines react with carbon tetrachloride.[3,4] Preliminary work showed that amines (marked * in Table) containing an NH group in aliphatic, or non-aromatic heterocyclic, systems react rapidly at room temperature with the deposition of crystalline

[1] Henbest, Meakins, Nicholls, and Wagland, *J.*, 1957, 1462.
[2] Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397.
[3] Russell and Thompson, *J.*, 1955, 483.
[4] Collins, *Chem. and Ind.*, 1957, 704.

material (? amine hydrochlorides). The other compounds in the Table did not react appreciably during the time needed for spectral examination.

The bands in the Table thought to be specifically associated with NMe and $NMe_2$ groups are in italics, and the amines are divided into four types according to the environment of the basic centre. Inspection of compounds 1 to 19 shows that amines possessing an NMe group attached to, or contained in, an aromatic system [type (I)] are distinguished from the reference compounds by a band occurring between 2820 and 2810 $cm.^{-1}$. The spectra shown in the Figure illustrate the ease with which the NMe group can be detected by the characteristic band on the low-frequency side of the main CH absorption. It is noteworthy that the band is not given by NEt groups [see *N*-ethylaniline (No. 2): note also that the NMe band's intensity in *N*-methylaniline (No. 3) is very close to that in *N*-ethyl-*N*-methylaniline (No. 4)].

With type (II) (Nos. 20—31) the overall distribution of CH bands between the frequency intervals shown in the Table differs from that of type (I). The main change, a higher proportion of bands with frequencies below *ca.* 2950 $cm.^{-1}$, is to be expected on passing from compounds with a high proportion of aromatic hydrogen to the reduced systems of the second type.[5] Despite this increased general absorption in the lower-frequency intervals the NMe group in aliphatic, or non-aromatic heterocyclic, systems can be recognised by a band between 2805 and 2780 $cm.^{-1}$. The alkaloids calycanthine [6] and folicanthine [7] [Nos. 30 and 31, partial structures (A) and (B) respectively] illustrate the possibility of application to natural products.




The intensities of the NMe bands in types (I) and (II) fall into two well-defined groups, and are much higher in the second type. It seems likely that the enhanced intensities of type (II) arise from the increased general absorption below 2950 $cm.^{-1}$ rather than from any appreciable change in the spectral properties of the NMe group. In folicanthine (B), with type (I) and type (II) NMe groups, it is presumably the second type which is mainly responsible for the absorption at 2795 $cm.^{-1}$.

The $NMe_2$ group directly attached to an aromatic system [type (III)] gives a band near 2800 $cm.^{-1}$, *i.e.*, very close to the position found with the corresponding monomethylamino-group [type (II)]. Thus the main consequence of replacing the hydrogen of an –NHMe group attached to an aromatic system by a second methyl group is to intensify the band ~2800 $cm.^{-1}$ [cf. *NN*-dimethylaniline (No. 33) and *N*-methylaniline (No. 3) in the Table and Figure: this effect supports the assignment of these bands to *N*-methyl vibrations]. Selection of the $NMe_2$ peak in *NN*-dimethyl-*o*-toluidine (No. 34) is difficult since it possesses two bands, one above and one below the expected frequency. This exceptional behaviour may be connected with substitution *ortho* to the dimethylamino-group.

When the $NMe_2$ group is not directly attached to an aromatic system [type (IV)] a new pattern emerges. Instead of intensification of the 2805—2780 $cm.^{-1}$ band in the corresponding monomethyl compounds [type (II)], two well-separated bands appear in the 2825—2810 and 2775—2765 $cm.^{-1}$ ranges. The strength of these bands, especially the lower-frequency components, makes detection of this type particularly easy, even in a complex molecule such as the cholesterol derivative (No. 42).

[5] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, pp. 13, 54.
[6] Robinson and Teuber, *Chem. and Ind.*, 1954, 783.
[7] Hodson and Smith, *J.*, 1957, 1877.

## CH *stretching bands (cm.$^{-1}$) of* NMe *compounds and, in square brackets, reference amines.*

Most of the compounds were examined in $CCl_4$ solution: for these molecular extinction coefficients (mole$^{-1}$ l. cm.$^{-1}$) are given in parentheses after the frequency values. Compounds marked * were examined as liquid films and the relative intensities of bands are indicated by s (strong) and m (medium). No intensity values are given for shoulders (sh) on the sides of main bands. All compounds were purified (by fractional distillation or crystallisation) immediately before being examined on a Perkin-Elmer model 21 spectrometer fitted with a calcium fluoride prism. The carbon tetrachloride used as solvent was washed repeatedly with alkali and then water, thoroughly dried and fractionated.

| No. | | 3100 | 3050 | 3000 | 2950 | 2900 | 2825 | 2800 | 2750 | 2700 |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Type (I).* NMe *attached to, or contained in, an aromatic system.* | | | | | | | | | |
| [1 | Aniline] | 3089(15)<br>3076(17) | 3039(40)<br>3015(17) | — | — | — | — | — | — | |
| [2 | *N*-Ethylaniline] | 3089(16)<br>3057(37) | 3023(31) | 2972(69) | 2930(31) | 2879(56) | — | — | — | |
| 3 | *N*-Methylaniline | 3088(15)<br>3055(36) | 3020(28) | 2983(25)<br>2950(21) | 2930(28)<br>2907(38) | 2883(35)<br>2861 sh | *2814(40)*<br>— | —<br>— | —<br>— | |
| 4 | *N*-Ethyl-*N*-methylaniline | 3095(23)<br>3056(30) | 3029(23) | 2973(>95) | 2934(56) | 2891(55)<br>2873(57) | *2817(40)*<br>2804 sh | — | — | |
| 5 | *N*-Methyl-*o*-toluidine | 3054(27) | 3018(28) | 2978(40) | 2927(50)<br>2910(53) | 2891(50)<br>2883 sh | *2816(42)* | — | — | |
| 6 | *N*-Methyl-*m*-toluidine | — | 3044(35)<br>3011(29) | 2979(39) | 2945 sh<br>2916(53) | 2889(44) | *2812(34)* | — | — | |
| 7 | *N*-Methyl-*p*-toluidine | — | 3046(28)<br>3028(43) | 2980(44) | 2921(67) | 2877(55) | *2813(41)* | — | — | |
| [8 | Diphenylamine] | 3090(27) | 3045(53)<br>3020(34) | — | — | — | — | — | — | |
| 9 | *N*-Methyldiphenylamine | 3088(31)<br>3065(42) | 3037(45)<br>3006 sh | — | 2942(25) | 2881(32) | *2814(28)* | — | — | |
| [10 | *N*-Benzyl-*N*-ethylaniline] | 3091(34)<br>3066(50) | 3031(57) | 2972(>75) | 2930(49) | 2896(40)<br>2875(44) | — | — | — | |
| 11 | *N*-Benzyl-*N*-methylaniline | 3090(32)<br>3066(48) | 3032(57) | 2980(24) | 2930(37) | 2897(44) | *2818(36)* | — | — | |
| [12 | α-Naphthylamine] | 3064(45)<br>3051 sh | 3020(21) | — | — | — | — | — | — | |
| 13 | *N*-Ethyl-α-naphthylamine] | 3066(50) | 3015(21) | 2974(67) | 2934(29) | 2876(42)<br>2856 sh | — | — | — | |
| 14 | *N*-Methyl-α-naphthylamine | 3067(52) | 3012(22) | 2985(27) | 2935(28)<br>2905(34) | 2884(35)<br>2845(19) | *2814(32)* | — | — | |
| [15 | Pyrrole] | No bands with $\varepsilon>10$ | | — | — | — | — | — | — | |
| [16 | *N*-Ethylpyrrole] | — | — | 2978(>50) | 2936(32)<br>2916(16) | 2884(20) | — | — | — | |
| 17 | *N*-Methylpyrrole | — | — | — | 2942(36)<br>2909(27) | — | *2811(12)* | — | — | |
| [18 | Indole] | 3083(20)<br>3059(28) | 3043(24)<br>3021(11) | — | — | — | — | — | — | |
| 19 | *N*-Methylindole | 3089 sh<br>3058(34) | 3032(20) | 2996(13) | 2946(34)<br>2913(28) | 2883(20) | *2817(14)* | — | — | |
| | *Type (II).* NMe *in an aliphatic, or a non-aromatic heterocyclic, system.* | | | | | | | | | |
| [20 | Diethanolamine] * | — | — | — | 2926 s | 2865 s<br>2848 s | — | — | — | |

| No. | | 3100 | 3050 | 3000 | 2950 | 2900 | 2825 | 2800 | 2750 | 2700 |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Type (II).* NMe *in an aliphatic, or a non-aromatic heterocyclic, system (continued).* | | | | | | | | | |
| 21 | *N*-Methyldiethanolamine | — | — | — | 2948(107) | 2877(99)<br>2844(81) | — | *2779(93)* | — | |
| [22 | Pyrrolidine] * | — | — | 2955 s | 2915 sh | 2868 s<br>2826 sh | — | — | — | |
| 23 | *N*-Methylpyrrolidine | — | — | 2966(142) | 2941(104)<br>2911(71) | 2881(59)<br>2836(69) | — | *2780(169)* | — | |
| [24 | Piperidine] * | — | — | — | 2931 s | 2854 s | 2805 s | — | 2737 m | |
| [25 | *N*-Ethylpiperidine] | — | — | 2971(110) | 2935(>235) | 2886(59)<br>2856(81) | 2802(104) | 2767(104)<br>2755 sh | 2731(52)<br>2703(32) | |
| 26 | *N*-Methylpiperidine | — | — | 2965(67) | 2936(>275) | 2888(60)<br>2856(94) | — | *2782(168)* | 2742(69)<br>2713(53) | |
| [27 | Morpholine] * | — | — | 2950 s | 2917 s | 2850 s | — | 2756 m | — | |
| [28 | *N*-Ethylmorpholine] | — | — | 2969(150) | 2940(98)<br>2923(87) | 2896(76)<br>2860(116) | 2811(133) | 2768(80) | 2732(27) | |
| 29 | *N*-Methylmorpholine | — | — | 2967(107) | 2940(110)<br>2916(86) | 2897(63)<br>2861(114) | —<br>— | *2798(160)*<br>2773(54) | 2749(38)<br>2740(38) | |
| 30 | Calycanthine (A) | 3079 sh<br>3052(61) | 3022(54) | 2964(118) | 2929(233)<br>2907 sh | 2857 sh<br>2843(129) | *2803(140)* | 2772(75) | 2742 sh<br>2702(21) | |
| 31 | Folicanthine (B) | 3069 sh | 3049(73) | 2962(209) | 2935(230)<br>2910(190) | 2866(174)<br>2851 sh | 2807 sh | *2795(190)* | — | |
| | *Type (III).* $NMe_2$ *directly attached to an aromatic system.* | | | | | | | | | |
| [32 | *NN*-Diethylaniline] | 3097(27)<br>3064(31) | 3028(36) | 2973(156) | 2932(79) | 2891 sh<br>2876(61) | 2825 sh | — | — | |
| 33 | *NN*-Dimethylaniline | 3097(22)<br>3069(27) | 3032(34) | 2985(37) | 2947(44) | 2897 sh<br>2848(51) | *2807(63)* | — | — | |
| 34 | *NN*-Dimethyl-*o*-toluidine | 3064(29) | 3019(39) | 2978(56) | 2941(102) | 2860(61)<br>*2826(88)* | — | *2785(77)* | — | |
| 35 | *NN*-Dimethyl-*m*-toluidine | 3079 sh | 3043(37) | 2975(52) | 2943(65)<br>2917(71) | 2883(65)<br>2851 sh | *2803(65)* | — | — | |
| 36 | *NN*-Dimethyl-*p*-toluidine | 3098(18)<br>3071(18) | 3007(46) | 2975(56) | 2942(69)<br>2917(79) | 2871(78) | — | *2797(67)* | — | |
| | *Type (IV).* $NMe_2$ *not directly attached to an aromatic system.* | | | | | | | | | |
| 37 | *iso*Butyldimethylamine | — | — | 2952(176) | 2910(87) | 2871(82)<br>2856(74) | *2816(104)* | *2767(138)* | 2723(42) | |
| 38 | 1 : 2-Bisdimethylaminoethane | — | — | 2970(127) | 2944(150) | 2860(99) | *2816(179)* | *2769(203)* | 2727(45) | |
| 39 | Gramine | 3083(22)<br>3059(39) | — | 2970(66) | 2941(91) | 2856(71) | *2813(113)* | *2770(153)* | 2720(34) | |
| 40 | *N*-Methylgramine | 3056(40) | 3033(23) | 2967(67) | 2942(111)<br>2915(71) | 2883(58)<br>2854(67) | *2815(105)* | *2769(137)* | 2728(31) | |
| 41 | " Mepyramine base " (C) | 3098(20)<br>3068(29) | 3005(65) | 2970(99) | 2945(125)<br>2909(88) | 2861(77)<br>2832(94) | *2821(109)* | *2774(125)* | 2732(25) | |
| 42 | 3α-Dimethylaminocholest-5-ene | — | 3044(24) | — | 2944(>580)<br>2906 sh | 2871(340) | *2812(162)* | *2772(214)* | — | |

By reasoning similar to that used with methyl ethers [1] the characteristic bands discussed above can be assigned to the symmetric CH stretching of $CH_3$ groups attached to nitrogen. Splitting of bands by vibrational coupling, such as that found with the second type of $NMe_2$ group [type (IV)], occurs frequently when two similar groups are attached to a common atom. It should be stressed that the NMe and $NMe_2$ correlations are confined at present to amines: preliminary work with substituted amides indicates that they may need modification in different structural types.

We are grateful to Miss S. Hackney for technical assistance, to Manchester University for a research scholarship (to R. D. H), to Dr. G. F. Smith for providing compounds **30** and **31**, to Dr. H. B. Henbest for compound **42**, and to Messrs. May and Baker Ltd. for compound **41**.

THE UNIVERSITY, MANCHESTER, 13. [*Received, August 7th,* 1957.]

---

## 149. *Chemical and Infrared Spectral Evidence for the Structure of Thiocyanogen Trichloride.*

By R. G. R. BACON, R. S. IRWIN, J. McC. POLLOCK, and A. D. E. PULLIN.

Thiocyanogen trichloride is prepared in good yield from solutions of thiocyanogen and excess of chlorine or, less satisfactorily, from sulphur dichloride and cyanogen chloride. When it decomposes, sulphur dichloride and cyanuric chloride are formed. It behaves as a sulphenyl chloride, $CNCl_2{\cdot}SCl$, and is related to compounds with the probable structures $(CNCl_2)_2S$ and $(CNCl_2{\cdot}S)_2$, preparations of which are described. Its behaviour towards salts (alkali-metal iodides, silver perchlorate, sodium *OO*-di-*n*-butyl thiophosphate) suggests that the group $CNCl_2$ is more likely to have the structure $NCl{:}CCl{\cdot}$ than $CCl_2{:}N{\cdot}$. Thiocyanogen trichloride adds to *cyclo*hexene to give 2-chloro*cyclo*hexyl dichlorothiocyanate, $C_6H_{10}Cl{\cdot}S{\cdot}CNCl_2$, reduction and oxidation of which are described.

The infrared spectrum has been obtained for the pure liquid, vapour, and solution from 4000 cm.$^{-1}$ down to 400 cm.$^{-1}$. The spectrum is noteworthy in that the band characteristic of C=N is absent, whereas a strong band at 1600 cm.$^{-1}$ is present which is assigned to a C=N group. The interpretation of the spectrum is based on a comparison with those of the chloroethylenes, to which spectra it is remarkably similar. This provides strong evidence for the two structures $Cl{\cdot}S{\cdot}CCl{:}NCl$ or $CCl_2{:}N{\cdot}S{\cdot}Cl$ although a distinction between these forms cannot be made.

FROM the interaction of thiocyanogen and chlorine in organic solvents Kaufmann and Liepe [1] obtained a solid, presumed to be monomeric thiocyanogen monochloride, but which Lecher and Joseph [2] and Baroni [3] showed to be polymeric $(SCNCl)_n$ ($n$ = *e.g.*, 2—6). We have shown [4] that the monomeric monochloride can in fact exist in organic solvents. With excess of chlorine Kaufmann and Liepe [1] obtained a relatively stable liquid, thiocyanogen trichloride, $SCNCl_3$, and this was confirmed by Baroni.[3] We now describe some chemical properties and the infrared absorption spectrum of the trichloride and discuss its structure in the light of the data now available.

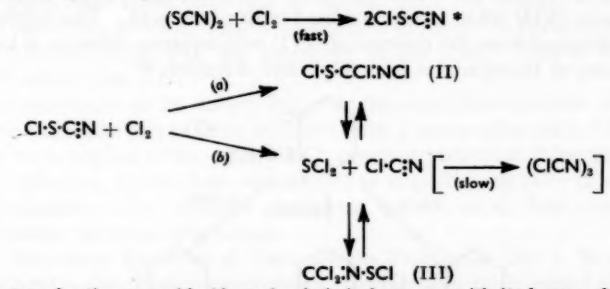
*Chemical Reactivity* (by R. G. R. BACON *and* R. S. IRWIN).—Kaufmann and Liepe formulated the trichloride as $SCl_3{\cdot}C{:}N$ (I), *i.e.*, as cyanosulphur trichloride. If this structure were correct the relatively stable nature of the compound would present a striking contrast with the instability of known quadrivalent sulphur derivatives containing chlorine atoms. Sulphur tetrachloride, $SCl_4$, is stated to be completely dissociated into $SCl_2$, $S_2Cl_2$, and $Cl_2$ in the liquid state.[5] Alkyl- and phenyl-sulphur trichlorides, $R{\cdot}SCl_3$, decompose

[1] Kaufmann and Liepe, *Ber.*, 1924, **57**, 923.
[2] Lecher and Joseph, *Ber.*, 1926, **59**, 2603.
[3] Baroni, *Atti R. Accad. Lincei*, 1936, **23**, 871.
[4] (*a*) Angus and Bacon, following paper; (*b*) Bacon and Irwin, *J.*, 1958, 778.
[5] Lowry, McHatton, and Jones, *J.*, 1927, 746; Lowry and Jessop, *J.*, 1929, 1421; 1930, 782.

at 5—25°,[6] and only in an analogous trifluoride, $R{\cdot}SF_3$, is stability found.[7] Likewise, various dichlorides of the type $RR'SCl_2$ are unstable.[8] Lately some experimental evidence against the formula (I) has been published by Fehér and Weber,[9] who found no band characteristic of the cyanide group in the Raman spectrum of thiocyanogen trichloride.

For this investigation we have not significantly deviated from Kaufmann and Liepe's preparative conditions; saturation of an ethyl bromide solution of thiocyanogen (~0·4M) with chlorine at room temperature or at 0°, followed by distillation, consistently gave the trichloride in yields of 70—80%. It is an orange, fuming liquid, which is preferably distilled under reduced pressure, but is reasonably stable at the b. p. (154°) at atmospheric pressure. Like sulphur monochloride and dichloride, it absorbs in both the visible and the near-ultraviolet regions, displaying a maximum at 345 mμ. The formula $SCNCl_3$ was confirmed by elementary analysis and from molecular weights obtained cryoscopically in benzene, ebullioscopically in carbon tetrachloride, and by the Victor Meyer vapour-density method. It reacted gradually and exothermically on shaking with cold water, giving numerous simple hydrolysis products, as noted by Kaufmann and Liepe,[1] and it reacted vigorously with alcohols. The pure compound could be preserved in stoppered vessels for many weeks, but decomposition was promoted by traces of impurities, such as result from exposure of the compound to water vapour. Its decomposition resulted in the formation of cyanuric chloride and sulphur dichloride; in a year-old sample decomposition had occurred to the extent of 60—70%.

The mode of preparation and the chemical reactions of thiocyanogen trichloride, which are further discussed below, suggest a structure (II) or (III), the former of which could theoretically exist as two geometrical isomers. The preparation may involve, as a first stage, production of the monochloride, which is a fast reaction,[4] followed by (*a*) addition of chlorine to the C≡N bond to give (II), or (*b*) chlorinolysis of the S–C bond in the monochloride to give sulphur dichloride and cyanogen chloride, which may then add to each other to give either (II) or (III).




(* This structure for the monochloride molecule is in harmony with its known chemical reactions, but the infrared absorption spectrum [4b] suggests that it does not satisfactorily represent the nature of the bonds.)

There are indications that the steps from mono- to tri-chloride are slower than formation of monochloride. For example, cryoscopic data indicated that 1 mole of thiocyanogen and 3 moles of chlorine were not transformed into the thiocyanogen trichloride stage in 0·1M-benzene solution at ~5°. We defer further comment on reaction rates until variations in preparative conditions have been examined. The validity of the above reaction scheme was demonstrated by an alternative preparation of thiocyanogen chloride, though in lower yield, by combination between sulphur dichloride and cyanogen chloride in cold ethyl

[6] Brower and Douglass, *J. Amer. Chem. Soc.*, 1951, **73**, 5787; Douglass, Brower, and Martin, *ibid.*, 1952, **74**, 5770.
[7] Chamberlain and N. Kharasch, *ibid.*, 1955, **77**, 1041.
[8] *E.g.*, Fries and Vogt, *Annalen*, 1911, **381**, 312, 337; Price and Smiles, *J.*, 1928, 2858; Hart, McClelland, and Fowkes, *J.*, 1938, 2114.
[9] Fehér and Weber, *Z. Naturforsch.*, 1956, **11b**, 426.

XUM

bromide. This was followed spectroscopically (see below). To take account of the observed mode of decomposition of thiocyanogen trichloride, the relation of (II) or (III) to cyanogen chloride and sulphur dichloride is represented as an equilibrium, which is disturbed by polymerisation of cyanogen chloride to cyanuric chloride, a process subject to catalysis.

A yellow liquid by-product, $C_2N_2Cl_4S$, appeared in yields of up to 20% in the preparation of thiocyanogen trichloride from thiocyanogen and chlorine. We regard this as sulphur bisdichlorocyanide (IV) and suggest its formation by an additional step:

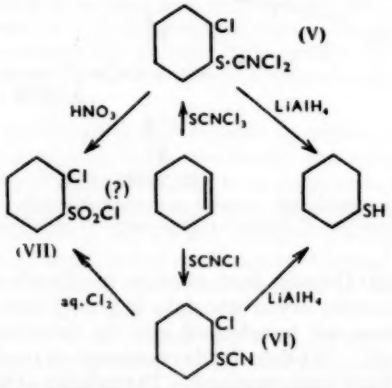
$$Cl{\cdot}C{\vdots}N + (II) \longrightarrow NCl{:}CCl{\cdot}S{\cdot}CCl{:}NCl \quad (IV)$$

or

$$Cl{\cdot}C{\vdots}N + (III) \longrightarrow CCl_2{:}N{\cdot}S{\cdot}N{:}CCl_2$$

The $CNCl_2$ groups are linked by sulphide bonds in the postulated structure (IV), just as they are linked by a disulphide group in the compound (VIII) (see below).

Both structures (II) and (III) can be summarised in the formula $CNCl_2{\cdot}SCl$. The compound might therefore by expected to show typical reactions of sulphenyl chlorides, such as addition to olefins:[10] $>C{=}C< + R{\cdot}SCl \longrightarrow >CCl{-}C(SR)<$. We found that thiocyanogen trichloride reacts vigorously with *cyclo*hexene to give the expected addition compound (V) containing the dichlorothiocyanato-group, a novel kind of substituent. To prove that this group is attached to the *cyclo*hexane ring through sulphur, the addition compound (V) was reduced by lithium aluminium hydride to *cyclo*hexanethiol. This thiol similarly resulted from reduction of 2-chloro*cyclo*hexyl thiocyanate (VI), the addition product[4a] of *cyclo*hexene and thiocyanogen monochloride. The removal of chlorine from the *cyclo*hexane ring in these reactions is interesting in view of the reported failure of *cyclo*hexyl chloride to be reduced by lithium aluminium hydride.[11] The cyclic sulphide of *cyclo*hexene may be an intermediate in the reduction of (V) and (VI),[12] and this sulphide is known to respond to lithium aluminium hydride.[13] A further indication of a linkage through sulphur in (V) was the isolation of what was almost certainly 2-chloro*cyclo*hexanesulphonyl chloride (VII) when it was oxidised with nitric acid. The sulphonyl chloride (VII) was also obtained from the thiocyanate (VI) with aqueous chlorine, a known reagent for the conversion of thiocyanates into sulphonyl chlorides:[14]




[10] N. Kharasch and co-workers, *J. Amer. Chem. Soc.*, 1947, **69**, 1612 and later papers; reviews by N. Kharasch, *J. Chem. Educ.*, 1956, **33**, 585, and N. Kharasch, Potempa, and Wehrmeister, *Chem. Reviews*, 1946, **39**, 269.

[11] J. E. Johnson, Blizzard, and Carhart, *J. Amer. Chem. Soc.*, 1948, **70**, 3664; cf. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publ., New York, 1956, p. 890.

[12] Cf. van Tamelen, *J. Amer. Chem. Soc.*, 1951, **73**, 3444.

[13] Mousseron, Jacquier, Mousseron-Canet, and Zagdoun, *Bull. Soc. chim. France*, 1952, **19**, 1042.

[14] T. B. Johnson and Douglass, *J. Amer. Chem. Soc.*, 1939, **61**, 2548; T. B. Johnson, *Proc. Nat. Acad. Sci.*, 1939, **25**, 448.

Pure samples of (V) were relatively stable, but cyanuric chloride and other polymers were gradually formed in impure samples and appeared immediately when the hot liquid was exposed to air. The thiocyanate (VI) could not be converted into the addition compound (V) by reaction with chlorine, or the reverse by reaction with zinc or potassium iodide.

The reactivity of halogen in thiocyanogen trichloride was examined in other ways. When aqueous potassium iodide was briefly shaken with a carbon tetrachloride solution of the trichloride, reaction was confined to the sulphur-linked chlorine atom, producing one equiv. of iodine and a moderately stable liquid, believed to be the disulphide, bisdichlorothiocyanogen (VIII):

$$2CNCl_2{\cdot}SCl + 2I^- \longrightarrow I_2 + 2Cl^- + CNCl_2{\cdot}S{\cdot}S{\cdot}CNCl_2 \quad \text{(VIII)}$$

This transformation is analogous to the known reaction of sulphenyl chlorides and iodide.[15] When the disulphide (VIII) decomposed, reaction appeared to take the course:

$$CNCl_2{\cdot}S{\cdot}S{\cdot}CNCl_2 \rightleftharpoons S_2Cl_2 + 2CNCl \; [\longrightarrow (CNCl)_2]$$

The reverse reaction was attempted by mixing sulphur monochloride and cyanogen chloride and this gave a small amount of a substance which, judged by the identity of infrared absorption spectra, was the disulphide (VIII). With iodide in acetic acid, the rapid liberation of 1 equiv. of iodine per mole of thiocyanogen trichloride was followed by slow liberation of a second equiv. With excess of silver perchlorate in benzene, not more than 2 equiv. of silver chloride were precipitated per mole of thiocyanogen trichloride. As a precipitation reagent we also used a benzene-soluble salt, sodium *OO*-di-*n*-butyl thiophosphate, $(Bu^nO)_2PO{\cdot}SNa$,[16] which we had studied in reactions with thiocyanogen monochloride.[4b] With thiocyanogen trichloride in benzene solution, excess of the salt produced a precipitate of not more than 2 equiv. of sodium chloride, reaction of the first chlorine atom being much more rapid than that of the second. The results of these experiments suggest high reactivity in a sulphur-bound chlorine atom of the trichloride, less reactivity in a second chlorine atom, and low reactivity in the third. This is in harmony with structure (II) rather than (III).

A general conclusion to be drawn from the chemical investigations is that a cyanide group can accommodate two chlorine atoms to form a reasonably stable $CNCl_2$ group when this is linked to a sulphur atom. The $CNCl_2$ group is present in thiocyanogen trichloride (a sulphenyl chloride), in its olefin adduct (V) (a sulphide), in (IV) (a sulphide), and in (VIII) (a disulphide). The infrared absorption spectra of all four compounds contain numerous common features (see below).

*Infrared Absorption Spectrum of Thiocyanogen Trichloride* (By J. McC. Pollock *and* A. D. E. Pullin).—The Raman spectrum of thiocyanogen trichloride [9] shows the Raman shifts listed in the first column of Table 1. For easy comparison the absorption bands found in our infrared study of the compound are given in the second column.

The most important feature of the infrared spectrum is the virtual absence of a band characteristic of the C≡N stretching vibration. This occurs around 2100 cm.$^{-1}$ and is found in the spectra of all organic thiocyanates,[17] cyanogen halides,[18] and the thiocyanate ion.[19] In liquid layers 0·1 mm. thick we have observed a very weak narrow band at 2145 cm.$^{-1}$ in all four preparations so far examined, but this is so weak (optical density ~0·08), being about 500 times weaker than the 1594 cm.$^{-1}$ band, that we do not consider it to be a fundamental of $SCNCl_3$. Although the intensity of the C≡N stretching band is known

[15] Orr and N. Kharasch, *J. Amer. Chem. Soc.*, 1953, **75**, 6030.
[16] Foss, *Acta Chem. Scand.*, 1947, **1**, 8; cf. Ref. 4*b*.
[17] Luskin, Gantert, and Craig, *J. Amer. Chem. Soc.*, 1956, **78**, 4965; Bacon and Guy, unpublished data.
[18] West and Farnsworth, *J. Chem. Phys.*, 1933, **1**, 402.
[19] Jones, *ibid.*, 1956, **25**, 1069.

to be variable, its absence from the infrared, together with Fehér and Weber's failure to observe it in their Raman work,[9] makes it very unlikely that thiocyanogen trichloride

TABLE 1.*

| $SCNCl_3$ | | | $CCl_3{\cdot}CHCl$ † | | $SCNCl_3$ | | $CCl_3{\cdot}CHCl$ † | |
|---|---|---|---|---|---|---|---|---|
| Raman | Infrared | | Raman | Infrared | Raman | Infrared | Raman | Infrared |
| 1604 (10) | 1603 (s) } | 1594 ‡ | 1586 (6) | 1585 (s) | 471 (7*d*) | 473 (vs) | 452 (3) | 452 (s) |
| 1587 (10) | 1589 (s) } | | | | 430 (1*d*) | 430 (w) | | |
| N.O. | 923 (vs) } | 913 ‡ | 933 (1) | 933 (s) | 385 (3) | N.E. | 380 (5) | N.E. |
| | 905 (vs) } | | | | 311 (2) | ,, | | ,, |
| 832 (1*d*) | 834 (m) | | 845 (~1) | 842 (s) | 275 (2) | ,, | 274 (5) | ,, |
| 757 (2) | 762 (w) | | | | 204 (7) | ,, | 211 (4) | ,, |
| 609 (2*d*) | N.O. | | 628 (5) | 630 (s) | | | 172 (5) | ,, |
| N.O. | 542 (ms) } | 529 ‡ | | | | | | |
| | 524 (vs) } | | | | | | | |

* N.O. = not observed; N.E. = not examined. † Less C–H frequencies.
‡ These bands are doublets. The figures so marked are the weighted mean frequencies of the pairs, the weighting being based on the relative infrared intensities of the two components in each case.

has the triple-bond structure (I). Our infrared spectra for the pure liquid, vapour, and solution in carbon tetrachloride from 4000 cm.$^{-1}$ to 400 cm.$^{-1}$ are reproduced in Fig. 1.

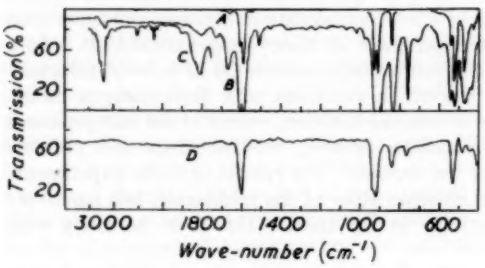



FIG. 1. *Spectra of* $SCNCl_3$. *Upper panel*: (*A*) *10% solution in* $CCl_4$, *0·017 mm. cell in the rock-salt region, 0·027 mm. cell in the* KBr *region*; (*B*) *liquid* $SCNCl_3$ *in the same cells*; (*C*) *liquid* $SCNCl_3$ *in a 0·1 mm. cell. Lower panel*: (*D*) *vapour spectrum, 18 cm. cell, equilibrium vapour pressure at room temperature* (~3·5 *mm.*).

From our interpretation of these spectra, it is possible to suggest two alternative structures (II) and (III); (II) is somewhat favoured on chemical grounds but our present spectroscopic evidence does not permit a distinction to be made between them. The strong band at 1600 cm.$^{-1}$ can only be explained by the presence of a C=N link, since $SCNCl_3$ is definitely monomeric under the experimental conditions. The C=S link is known to absorb at much lower frequencies, usually between 1100 and 1350 cm.$^{-1}$,[20] and the system ·N:C:S, like O:C:S, gives absorption bands above 2000 cm.$^{-1}$. A compound R·S·CCl:NR′ [R = 2 : 4-$C_6H_3(NO_2)_2$, R′ = *p*-$C_6H_4Me$], having a similar skeleton to that suggested for $SCNCl_3$, has a strong absorption band at 6μ, attributed to a C=N bond.[21]

For comparison of the spectrum of $SCNCl_3$ with those of related compounds, there do not appear to be any data on chlorine-substituted C=N systems. However, the spectra of $NH_2Cl$, $NHCl_2$, and $NCl_3$ are known,[22] and in these compounds the N–Cl stretching frequencies are very similar to those of the related carbon compounds. On this basis, the structures suggested for thiocyanogen trichloride may be compared with the chlorine-substituted ethylenes.

It is clear from Table 1 that there is a close similarity between the spectra of thiocyanogen trichloride and of trichloroethylene [23] with respect to both frequencies and

[20] Mecke and Lüttringhaus, *Z. Naturforsch.*, 1955, **10***b*, 367.
[21] Havlik and Walk, *J. Amer. Chem. Soc.*, 1955, **77**, 5171.
[22] Moore and Badger, *ibid.*, 1952, **74**, 6076.
[23] Allen and Bernstein, *Canad. J. Chem.*, 1954, **32**, 1044.

intensities. In view of the similarities of the disposition of atomic masses and force constants between the structures (II) and (III) and trichloroethylene, this affords strong evidence for these structures.* Distinction between the structures (II) and (III) on spectroscopic grounds does not yet seem possible. The spectral data for $CF_2{:}CCl_2$,[24] $CHCl{:}CCl_2$,[23] and *cis*- and *trans*-$CHCl{:}CHCl$ [25,26] suggest that a C–Cl stretching motion only gives rise to bands above 900 cm.$^{-1}$ in the antisymmetric stretching mode of a $=CCl_2$ group. This fact, however, does not necessitate assigning structure (III) to thiocyanogen trichloride in order to account for the 913 cm.$^{-1}$ band. Organic sulphides R·S·R give frequencies very close to those of the corresponding halides RCl,[27] so that interaction between the C–Cl and C–S stretching motions should occur in structure (II), making it, like structure (III), dynamically similar to trichloroethylene.

Because of the low symmetry of structure (II) or (III), and the strong interaction expected between the individual bond-stretching motions, it is not profitable to try to assign completely the bands to definite vibrational modes. It is probable that the 913 cm.$^{-1}$ band corresponds approximately to an antisymmetric stretching mode of the carbon single bonds. The band at 529 cm.$^{-1}$ may arise largely from S–Cl stretching motion (in $CCl_3$·SCl a Raman shift of 536 cm.$^{-1}$ is assigned to the S–Cl stretching mode,[28] while in $SCl_2$ the S–Cl stretching vibrations occur [29] at 436 and 516 cm.$^{-1}$), although, structure (III) being assumed, an alternative assignment to an N–S stretching mode is possible, as the N–S link gives bands in the 550 cm.$^{-1}$ region.[30]

The spectra afford strong evidence for the presence of more than one structure in the samples of thiocyanogen trichloride. It is evident, *e.g.*, from Table 1, that, the splitting of the major bands being disregarded, thiocyanogen trichloride shows one or possibly two bands more, in the bond-stretching region, than can be attributed to fundamental bands of a single structure, and since it does not seem possible to account for any of these bands as combination tones, the presence of more than one structure must be assumed. We have demonstrated the formation of thiocyanogen trichloride from sulphur dichloride and cyanogen chloride in ethyl bromide solution spectroscopically, by observing the increase in intensity with time of the two doublet bands at 1603, 1589, and 923, 905 cm.$^{-1}$. Spectra taken at different time intervals for a reaction mixture at 0° are shown in Fig. 2. This demonstrates the production of thiocyanogen trichloride, in agreement with the reversible reaction scheme on p. 765. The additional absorption band or bands in the spectrum of thiocyanogen trichloride may be due to other species in equilibrium with $SCNCl_3$.

The infrared spectra of the related compounds (IV), (V), and (VIII) have been obtained in the rock-salt region (Figs. 3 and 4). The spectra of the sulphide (IV) and the disulphide (VIII) are very similar to that of thiocyanogen trichloride, and in each case there is no absorption in the 2100—2200 cm.$^{-1}$ region. As might be expected, the spectrum of the disulphide (VIII), in which the two $CNCl_2$ groups are linked by a disulphide unit is more similar to that of thiocyanogen trichloride than that of the sulphide (IV). In (VIII) the bands corresponding to the 1594 and the 757 cm.$^{-1}$ band of thiocyanogen trichloride are both displaced to lower frequencies (1588 and 735 cm.$^{-1}$). In (IV) the corresponding lower-frequency band is at 777 cm.$^{-1}$. Neither the sulphide (IV) nor the disulphide (VIII) shows a band of comparable intensity to the moderately strong band in thiocyanogen

* In $CDCl{:}CCl_2$ the 933 cm.$^{-1}$ band is replaced by a band at 876 cm.$^{-1}$; here, as in the other chlorine-substituted ethylenes, the interaction between the C–D bending and C–Cl stretching motions has lowered the frequency of the C–Cl stretching mode, so that the comparison with the spectra of $CHCl{:}CCl_2$, as in Table 1, rather than with $CDCl{:}CCl_2$, is more appropriate.

[24] Nielsen and Claassen, *J. Chem. Phys.*, 1950, **18**, 485.
[25] Bernstein and Ramsay, *ibid.*, 1949, **17**, 556.
[26] Bernstein and Pullin, *Canad. J. Chem.*, 1952, **30**, 963.
[27] Sheppard, *Trans. Faraday Soc.*, 1950, **46**, 429.
[28] Fehér and Berthold, *Z. anorg. Chem.*, 1956, **284**, 60.
[29] Clara Otero and José R. Barceló Matutano, *Anal. Fís. Quím.*, 1956, **52**, *B*, 291.
[30] Hofmann and Andress, *Z. anorg. Chem.*, 1956, **284**, 234.

XUM

trichloride at 834 cm.$^{-1}$. The similarity of the spectra of thiocyanogen trichloride, (IV), (V), and (VIII) extends to the combination tones and overtones. Table 2 shows the probable attribution of the stronger infrared combination tones. For thiocyanogen trichloride the uncertainty with regard to resonance splitting of the combination levels which involve the 913 cm.$^{-1}$ fundamental makes the attributions less sure.

FIG. 2. *Formation of* $SCNCl_3$ *from* $SCl_3$ *and* ClCN *in ethyl bromide solution at 0°: equivalent quantities of* $SCl_3$ *and* ClCN, *solution 50% by volume in ethyl bromide, 0·1 mm. cell.*

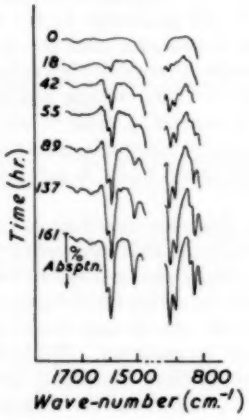
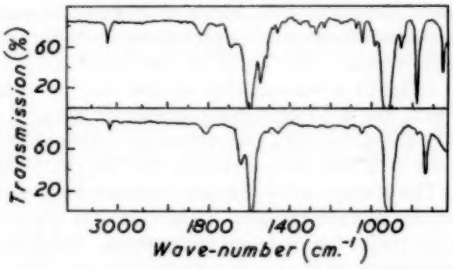



FIG. 3. *Upper panel: spectrum of liquid film of* (IV), i.e., $(CNCl_2)_2S$. *Lower panel: spectrum of liquid film of* (VIII), i.e., $(CNCl_2)_2S_2$.



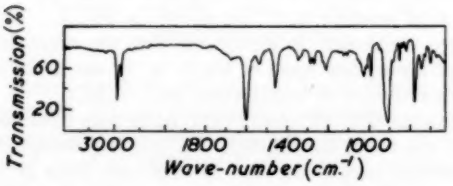




FIG. 4. *Spectrum of liquid film of* (V), i.e., *adduct of* cyclo*hexene and* $SCNCl_3$.

The spectrum of the addition compound (V) is more complex than those of thiocyanogen trichloride or structures (IV) and (VIII). The strongest bands in the rock-salt region are at 2935, 1597, 908, and 775 cm.$^{-1}$.

Slight further support for the presence of more than one structure in the samples of

TABLE 2.

| Thiocyanogen trichloride | | (IV) | | (VIII) | | (V) | |
|---|---|---|---|---|---|---|---|
| 3270 | 1594 + 1665 = 3259 | | | | | | |
| 3180 | 2 × 1594 = 3188 | 3185 | 2 × 1597 = 3194 | 3145 | 2 × 1588 = 3176 | 3175 | 2 × 1597 = 3194 |
| 1840 (sh) | 2 × 923 = 1846 | 1833 | 2 × 923 = 1846 | 1813 | 2 × 914 = 1828 | 1805 | 2 × 908 = 1816 |
| 1805 | 2 × 905 = 1810 | | | | | | |
| 1665 | 913 + 757 = 1670 | 1687 | 923 + 777 = 1700 | 1640 | 914 + 735 = 1649 | 1675 | 908 + 775 = 1683 |
| | 2 × 832 = 1664 | | | | | | |
| 1506 | 2 × 757 = 1514 | 1543 | 2 × 777 = 1554 | 1460 | 2 × 735 = 1470 | 1533 | 2 × 775 = 1550 |

thiocyanogen trichloride investigated is afforded by the splitting of the fundamental band at 1594 cm.$^{-1}$. The combination tone 757 + 832 = 1589 is a little lower than is required to give rise to the two components at 1589 and 1604 cm.$^{-1}$ by Fermi resonance,

which suggests that the two components of the 1594 cm.$^{-1}$ band are due to the presence of two distinct structures. The splitting of the 913 cm.$^{-1}$ band can be accounted for by interaction with the combination tone $609 + 311 = 920$. It seems likely that several low-lying fundamentals have not been observed. In particular there should be a fundamental corresponding to the C–S–Cl (or N–S–Cl) in plane bending. In $CCl_3$·SCl a frequency of 131 cm.$^{-1}$ was attributed [28] to the C–S–Cl deformation mode. A fundamental at about this frequency could provide an explanation of the splitting of the 529 cm.$^{-1}$ band (*e.g.*, $385 + 144 = 529$). There is, however, the possibility of rotational isomerism due to different orientations of the S–Cl group.

## Experimental

*Thiocyanogen Trichloride.*—(*a*) Bromine (0·1 mole) was rapidly decolorised when stirred at room temperature with lead thiocyanate (0·105 mole) in ethyl bromide (~250 ml.). The resulting thiocyanogen solution was separated from lead salts and treated with a stream of dry chlorine until saturated (periods of up to 1 hr.) at room temp. or at 0°. An orange colour developed. After removal of solvent and excess of chlorine at ~10°/20 mm., thiocyanogen trichloride was collected in yields of 11—13 g. (70—80%) as a pungent orange liquid, b. p. 40—41°/9 mm., which distilled at 154—155°/1 atm. with very little decomposition; Kaufmann and Liepe [1] give b. p. 54—56°/20 mm., 152—153°/1 atm. (Found: C, 7·8; N, 8·1; S, 19·1; Cl, 64·4. Calc. for $CNCl_3S$: C, 7·3; N, 8·5; S, 19·4; Cl, 64·7%). A pungent yellow liquid, regarded as *sulphur bisdichlorocyanide* (IV), b. p. 50°/0·2 mm., was also obtained in these preparations as a clean-cut fraction (1—3 g.) (Found: C, 10·9; N, 12·3; S, 13·6; Cl, 63·4. $C_2N_2Cl_4S$ requires C, 10·6; N, 12·4; S, 14·1; Cl, 62·8%). (*b*) Sulphur dichloride, b. p. 59°, was prepared as described by Bothamley.[31] Cyanogen chloride (12 g.) from a cylinder (Imperial Chemical Industries Limited) was condensed into ethyl bromide (40 ml.) containing sulphur dichloride (3 g.) and the solution was kept at 0° for 5 days. Thiocyanogen trichloride (1·3 g., 27%), b. p. 50—51°/18 mm., was isolated as in method (*a*) and was converted into 2-chloro-*cyclo*hexyl dichlorothiocyanate (V), identical in infrared absorption spectrum with the product obtained (see below) by using the thiocyanogen trichloride obtained by method (*a*).

*Decomposition Products.*—Carefully redistilled thiocyanogen trichloride remained unchanged for many weeks in sealed vessels. Decomposition, particularly marked in impure samples, was shown by deposition of cyanuric chloride, m. p. 145° (Found: C, 20·0; N, 22·7; Cl, 57·7. Calc. for $C_3N_3Cl_3$: C, 19·5; N, 22·7; Cl, 57·75%). A reasonably pure sample of the trichloride, which had been stored in the dark in a stoppered bottle for about one year, had deposited 61% of the theoretical amount of cyanuric chloride; the liquid residue yielded sulphur dichloride, b. p. 59°/1 atm., as a dark red fuming liquid (70%), and a little unchanged thiocyanogen trichloride.

*Hydrolysis Products.*—Thiocyanogen trichloride was completely hydrolysed, exothermically, by shaking with about ten times its weight of cold water for about 1 hr. Sulphur was deposited. The pale yellow, acidic, aqueous solution responded strongly to qualitative tests for cyanogen chloride, hydrogen sulphide, and sulphate and chloride ions, responded weakly to tests for cyanide, thiocyanate, and sulphite ions, and gave weak indications of ammonia when warmed with alkali.

*Reaction with Silver Perchlorate.*—When 25 ml. portions of a benzene solution of silver perchlorate (0·10M) were treated with suitable proportions (see below) of a benzene solution of thiocyanogen trichloride (0·17M), during about 3 min. at room temp., the weight of precipitate deviated from the expected figure for silver chloride by ±10%. Use of restricted amounts of thiocyanogen trichloride showed that not more than two-thirds of its chlorine could be thus utilised; 1 mol. of $SCNCl_3$ + 1·0, 2·0, or 3·0 mol. of $AgClO_4$ gave 1·0, 2·0, and 2·0 mol. of AgCl, respectively. In the experiment at a 1 : 2 molar ratio the filtrate from the silver chloride gave no response with a fresh portion of silver perchlorate.

*Reaction with Sodium* OO-*Di*-n-*butyl Thiophosphate.*—This salt was prepared as previously described.[4b] Solutions in carbon tetrachloride (~0·1M), when mixed with solutions of thiocyanogen trichloride in carbon tetrachloride (~0·1M), yielded precipitates of sodium chloride

[31] Bothamley, *Trans. Faraday Soc.*, 1928, **24**, 47.

which sometimes contained a little organic matter but were free from thiocyanate; they were 97—100% pure by titration; 1·0 mol. of $SCNCl_3$ + 1·0 mol. of $(BuO)_2POSNa$ gave 0·97 mol. of NaCl in a few minutes. The filtrate, treated with a further 1·0 mol. of $(BuO)_2POSNa$, reacted slowly to give a fine precipitate and required several hours before yielding a further 1·07 mol. of NaCl in coagulated form. A similar result was obtained by mixing 1·0 mol. of $SCNCl_3$ + 2·0 mol. of $(BuO)_2POSNa$ (yield, 1·96 mol. of NaCl). With 1·0 mol. of $SCNCl_3$ + 3 or more mol. of $(BuO)_2POSNa$ the fine precipitate remained in suspension, coagulation presumably being prevented by the unchanged sodium dibutyl thiophosphate.

*Reaction with Sodium or Potassium Iodide.*—(i) 0·1M-Solutions of thiocyanogen trichloride in carbon tetrachloride were shaken for 3 min. with excess of 10% aqueous potassium iodide and the liberated iodine was estimated with thiosulphate. An average of 0·975 equiv. of iodine was found per mole of thiocyanogen trichloride. (ii) 0·1M-Solutions of thiocyanogen trichloride in dry acetic acid (5% of acetic anhydride present) liberated iodine when treated at room temperature with excess of 5% potassium iodide solution in the same solvent. The titre after 3 min. corresponded with 1·03 equiv. of iodine per mole of thiocyanogen trichloride and thereafter rose very slowly towards 2 equiv. per mole. Under similar conditions, but using sodium iodide, which Orr and Kharasch [15] found to react more rapidly than potassium iodide with sulphenyl chlorides, 2·03 equiv. of iodine per mole were liberated after 3 minutes' reaction. Sulphur and cyanogen chloride were detected in this reaction.

*Bisdichlorothiocyanogen* (VIII).—(*a*) Thiocyanogen trichloride (6·0 g.) in carbon tetrachloride (50 ml.) was vigorously shaken for 3 min. with a large excess of aqueous potassium iodide (30 g. in 50 ml. of water). The liberated iodine was immediately removed with aqueous thiosulphate and the decolorised organic layer was separated, filtered from deposited sulphur, dried, and distilled; the reaction product, now a red oil, yielded *bisdichlorothiocyanogen* (VIII) as a pale yellow liquid with no fume and little odour (2·1 g., 45%), b. p. 64—68°/0·15 mm. (Found: C, 9·3; N, 10·6; S, 24·4; Cl, 54·6. $C_2N_2Cl_4S_2$ requires C, 9·3; N, 10·8; S, 24·8; Cl, 55·1%). One rather impure sample of this product decomposed during 4 days at room temp., depositing cyanuric chloride, m. p. and mixed m. p. 146°, and leaving a yellow oil, b. p. 136°, with the characteristic odour of sulphur monochloride.

(*b*) Sulphur monochloride (3·0 g.) and excess of cyanogen chloride (12 g.) in dry ethyl bromide (40 ml.) were kept for 6 days in the dark at 0°. After removal of solvent and unchanged reagents at 20 mm. pressure, there remained a small amount of yellow oil which yielded a fraction (0·54 g., 10%), b. p. 76—78°/0·4 mm.; this showed an infrared absorption spectrum identical with that shown by the product of method (*a*).

2-*Chloro*cyclo*hexyl Dichlorothiocyanate* (V).—Thiocyanogen trichloride (10 g.) in carbon tetrachloride (40 ml.) was treated during ~20 min. with excess of *cyclo*hexene (15 g., 3 mol.) in carbon tetrachloride (10 ml.). The temperature rose to ~60° and the colour of the reagent disappeared. Distillation yielded 2-*chloro*cyclo*hexyl dichlorothiocyanate* (V) (12·0 g., 80%), as a colourless oil, b. p. 80—82°/0·1 mm., $n_D^{25}$ 1·5620, with a sweetish but disagreeable odour (Found: C, 34·35; H, 3·8; N, 5·8; S, 12·8; Cl, 43·15. $C_7H_{10}NCl_3S$ requires C, 34·1; H, 4·1; N, 5·7; S, 13·0; Cl, 43·15%). It was not obtained when 2-chloro*cyclo*hexyl thiocyanate (VI) [4a] was treated with excess of chlorine in ethyl bromide. It was characterised by its infrared absorption spectrum (p. 770) and by its reduction and oxidation products (see below). Pure samples underwent no change during storage for several weeks, but impurities promoted decomposition to cyanuric chloride, amorphous white solid, and oils of higher b. p. (*e.g.*, 80—130°/0·1 mm.). It appeared to be largely unchanged after 2 hours' heating with powdered zinc at 100°. It liberated iodine when shaken (3 min.) with sodium iodide in acetic acid, but no organic reaction product was isolated.

cyclo*Hexanethiol*.—(*a*) 2-Chloro*cyclo*hexyl dichlorothiocyanate (V) (4·9 g., 0·02 mole) was slowly treated in ether with lithium aluminium hydride (0·04 mole). Reaction was completed by refluxing (2 hr.), the product decomposed with water, and the dried ethereal solution distilled, to yield *cyclo*hexanethiol (0·55 g., 24%), b. p. 158—160°/1 atm. (lit. 158—160°). It was characterised as 1-*cyclo*hexylthio-2 : 4-dinitrobenzene, m. p. 148°, as quoted by Bost, Turner, and Conn [33] (Found: C, 51·15; H, 5·0; N, 10·15; S, 11·0. Calc. for $C_{12}H_{14}O_4N_2S$: C, 51·1; H, 5·0; N, 9·9; S, 11·3%).

(*b*) Reduction was carried out similarly, by use of 2-chloro*cyclo*hexyl thiocyanate (VI) [4a] (0·02 mole) and lithium aluminium hydride (0·03 mole). An ammoniacal odour was noted.

[33] Bost, Turner, and Conn, *J. Amer. Chem. Soc.*, 1933, **55**, 4956.

*cyclo*Hexanethiol was obtained in 30% yield and characterised as 1-*cyclo*hexylthio-2 : 4-dinitrobenzene, m. p. and mixed m. p. with the sample from method (*a*) 148°. A liquid fraction, b. p. 56—57°/15 mm., obtained in one experiment, may have contained *cyclo*hexene thioepoxide; it reacted with methyl iodide, as described for the thioepoxide by van Tamelen.[12]

cyclo*Hexanesulphonyl Chloride* (VII).—2-Chloro*cyclo*hexyl dichlorothiocyanate (V) (4·9 g., 0·02 mole) reacted very vigorously when added dropwise to fuming nitric acid (7·5 ml.), cooled by an ice–salt bath. After 2 days at room temperature the product was added to ice, and the oil which separated was ether-extracted and distilled, yielding a well-defined fraction (0·64 g., 15%), b. p. 72°/0·1 mm., $n_D^{16}$ 1·5180, probably 2-*chloro*cyclo*hexanesulphonyl chloride* (VII) (Found: C, 33·4; H, 4·3; S, 14·6; Cl, 32·6. $C_6H_{10}O_2Cl_2S$ requires C, 33·2; H, 4·6; S, 14·8; Cl, 32·7%). It resisted hydrolysis, but after boiling with water for 23 hr. the solution of sulphonic acid yielded a *S*-benzylthiuronium salt, m. p. 150—151°, which was not analytically pure. Preparation of (VII) was attempted by treating 2-chloro*cyclo*hexyl thiocyanate (VI) in water with a stream of chlorine, following the general procedure of Johnson and Douglass.[14] The product (42% yield) closely resembled that described above, but was not analytically pure. The infrared absorption spectrum of a liquid film showed very strong bands at 1165 and 1378 cm.$^{-1}$, attributed to $SO_2Cl$, medium bands at 740 and 754 cm.$^{-1}$, attributed to CCl, and other main bands at 2948 (s), 2869 (m), 2164 (w), 1458 (s), 1287 (m), 1266 (w), 1206 (m), 1125 (w), 911 (w), and 817 cm.$^{-1}$ (w).

*Cryoscopic Data.*—These were obtained as described for thiocyanogen monochloride.[4b] (i) In benzene solution (1—2%) the average f. p. depression indicated a molecular weight of 159 ($CNCl_2S$ requires *M*, 164·5). (ii) Benzene solutions of chlorine and thiocyanogen (~0·1M) were mixed in a 3 : 1 molar ratio. Found f. p. depression, 0·538°; calc. for $3Cl_2 + (SCN)_2$ or $2Cl_2 + 2SCNCl$, 0·547°; calc. for $2SCNCl_3$, 0·274°. (iii) Benzene solutions of thiocyanogen and thiocyanogen trichloride (~0·1M) were mixed in a 1 : 1 molar ratio. Found f. p. depression, 0·745°; calc. for no reaction, 0·777°; calc. for $SCNCl_3 + (SCN)_2 \longrightarrow 3SCNCl$, 1·166°.

*Ebullioscopic Data.*—In carbon tetrachloride, on use of a modified Cottrell apparatus,[33] the average elevation of b. p. indicated a molecular weight of 171.

*Vapour Density.*—In a conventional type of Victor Meyer apparatus, heated by boiling ethylene glycol, vapour density measurements indicated a molecular weight of 160.

*Ultraviolet Absorption Spectra.*—A Unicam S.P. 500 instrument was used. Absorption in the visible and the near-ultraviolet regions, by carbon tetrachloride solutions, was limited to the region above ~280 mμ. With thiocyanogen trichloride, absorption began at 480 mμ and reached a maximum at 345 mμ (log ε 1·93). With sulphur dichloride, absorption began at 450 mμ and reached no maximum but showed an inflection at 310 mμ (log ε 2·40). With sulphur monochloride, absorption began at 410 mμ and reached a maximum at 304 mμ (log ε 3·06).

*Infrared Absorption Spectra.*—Thiocyanogen trichloride was fractionated with a 12″ jacketed column filled with glass helices; $SCNCl_3$ was collected at 50—51°/18 mm. A number of separate preparations were examined. The spectra were taken with a Perkin-Elmer Model 21 double-beam spectrophotometer, NaCl and KBr prisms being used. Water vapour, carbon dioxide, and ammonia bands were used for calibration. Spectra were taken as soon as possible after the liquid was fractionated (usually within about 10 min.) in order to avoid decomposition, although pure samples kept in a dry atmosphere for a month showed only very slight traces of decomposition. The vapour spectra were taken with 18 cm. cells, at room temperature (estimated vapour pressure 3·5 mm.). The vapour readily attacked several cements used for fixing the windows to the cells, giving spurious peaks after a few minutes. Eventually Bakelite cement No. J 11185 was found to be satisfactory at least for reasonable periods.

QUEEN'S UNIVERSITY, BELFAST. [*Received, July 22nd*, 1957.]

[33] Linstead, Elvidge, and Whalley, "Modern Techniques in Organic Chemistry," Butterworths, London, 1955, p. 148.

XUM

## 150. *Thiocyanogen Chloride. Part I. Chemical Evidence for the Existence of the Monomeric Compound in Solutions in Organic Solvents.*

By A. B. Angus and R. G. R. Bacon.

Whereas previous descriptions of thiocyanogen chloride refer to relatively inert polymeric solids, the behaviour of fresh solutions made with equimolecular proportions of thiocyanogen and chlorine now suggests that they contain the reactive monomeric species Cl·S·CN. This adds immediately to olefins; in the case of ethylene and *cyclo*hexene the 2-chloroalkyl thiocyanate is thus obtained in high yield. With suitably reactive aromatic compounds it gives aryl thiocyanates, in good yield, and hydrogen chloride. Its reactivity towards dimethylaniline, phenol, and anisole is assessed in comparison with that of thiocyanogen and chlorine. Its observed properties suggest a compound polarised in the manner of $\overset{\delta-}{Cl}–\overset{\delta+}{SCN}$, with reactivity intermediate between that of chlorine and thiocyanogen and comparable with that of iodine chloride.

Compounds formed between halogens and pseudohalogens have been little investigated.[1] Thiocyanogen monochloride is such a compound. The parent pseudohalogen $(SCN)_2$, discovered by Söderbäck,[2] possesses many properties intermediate between those of bromine and iodine.[3] Thiocyanogen chloride might therefore be expected to show similar reactivity to iodine monochloride and bromine monochloride; such properties are now described.

A substance of the analysis SCNCl was isolated by Kaufmann and Liepe [4] after treating thiocyanogen with chlorine in halogenated hydrocarbons at about 0°. Since it was a crystalline solid, stable up to about 150°, and with very little chemical reactivity, it was evidently a polymer. This view was taken by Lecher and Joseph,[5] whose results suggested that the products made by Kaufmann's method were approximately hexameric, and by Baroni,[6] whose products were at least dimeric, even when made at −60°. Kaufmann's claim [7] that " thiocyanogen chloride " is monomeric when redissolved in boiling chloroform remains unconfirmed, though it is possible that the polymers can undergo some form of degeneration in hot organic solvents, for Lecher and Joseph used their polymer to convert dimethylaniline into *p*-thiocyanatodimethylaniline at 70—80°. The reaction of excess of chlorine with thiocyanogen produces a trichloride,[8] and decomposition reactions may produce sulphur chlorides and cyanuric chloride.

Seel and Müller [9] recently isolated thiocyanogen monobromide from sulphur dioxide solvent at −50° as a red, volatile, dissociable, and highly reactive crystalline solid. We have not tried to improve on the attempts of earlier workers to isolate the monomeric monochloride, but have examined the properties of the solutions obtained by mixing thiocyanogen and chlorine in organic solvents. These show the expected properties of solutions of Cl·SCN molecules. Their preparative applications have been indicated recently,[10] some of their physical properties are described in Part II (following paper), and

[1] Sharpe, *Quart. Rev.*, 1950, **4**, 115.
[2] Söderbäck, *Annalen*, 1919, **419**, 217.
[3] Reviewed by Wood, " Organic Reactions," Vol. 3, Wiley, New York, 1946, p. 240.
[4] Kaufmann and Liepe, *Ber.*, 1924, **57**, 923.
[5] Lecher and Joseph, *Ber.*, 1926, **59**, 2603.
[6] Baroni, *Atti R. Accad. Lincei*, 1936, **23**, 871.
[7] Kaufmann, *Ber.*, 1927, **60**, 58.
[8] Bacon, Irwin, Pollock, and Pullin, preceding paper.
[9] Seel and Müller, *Chem. Ber.*, 1955, **88**, 1747.
[10] Angus, Bacon, and Guy, *Chem. and Ind.*, 1955, 564.

XUM

various reactions will be reported later. We now describe two groups of experiments which first showed that Cl·SCN molecules add to olefinic bonds and cause thiocyanation of aromatic rings.*

We treated thiocyanogen solutions [2,3] with an equimolecular proportion of dissolved or gaseous chlorine. An immediate change in odour and colour occurs, the temperature rises slightly and the solution exhibits new physical and chemical properties. These changes we ascribe to the reaction: $(SCN)_2 + Cl_2 \longrightarrow 2Cl{\cdot}SCN$. The product is estimated iodometrically, like thiocyanogen or chlorine, through its instantaneous reaction with potassium iodide: $Cl{\cdot}SCN + 2I^- \longrightarrow SCN^- + Cl^- + I_2$. The titre of freshly prepared mixtures in dry purified solvents is typically 95—98% of the value to be expected from the titre of the components; lower figures are found if impure solvents are used. This deficiency could be due to side-reactions or to the consumption of some thiocyanogen chloride through reactions with contaminants or through polymerisation. The small loss in titre on mixing appears to be immediate, but there is a further and gradual deterioration, dependent on solvent, concentration, temperature, and illumination, which occurs when solutions are stored. Nevertheless, solutions can readily be prepared which show the reactions of thiocyanogen chloride during several days at 0—20°; they should be titrated just before use. In general, the preferred concentration range for reasonably stable solutions is 0·1—0·4N (0·05—0·2M)-Cl·SCN.

The choice of solvent is influenced by (*a*) its suitability as a medium for the reaction of thiocyanate and halogen,[2,3] (*b*) stability of the thiocyanogen solution thus produced, (*c*) the stability of the thiocyanogen chloride solution obtained by subsequent reaction with chlorine, and (*d*) the influence of the solvent on the reactions of the thiocyanogen chloride with organic compounds. Carbon tetrachloride was used in some experiments because it contains no replaceable hydrogen. It has limitations if, *e.g.*, 0·5—1N-thiocyanogen solutions are desired as a starting point, since the solution then obtained from lead thiocyanate and bromine is weaker than expected, rapidly declines in strength to ~0·4N-$(SCN)_2$, and is often accompanied by highly unstable material, possibly undissolved thiocyanogen, in the residual lead salts. We also employed chloroform, preferably freed from ethanol. This was used by earlier workers for thiocyanogen chloride preparations; it is an excellent medium for the preparation of thiocyanogen and was found satisfactory for relatively concentrated reagent (2M-Cl·SCN) at low temperatures. Toluene was also used, because it remains liquid at low temperatures, but it is too reactive towards thiocyanogen chloride to be generally recommended.

Addition of an olefin to thiocyanogen chloride solution causes an immediate exothermic reaction in which an α-chloro-β-thiocyanato-compound is produced: $>C{:}C< + Cl{\cdot}SCN \longrightarrow >CCl{\cdot}C(SCN)<$. Ethylene and *cyclo*hexene thus gave, respectively, the known 2-chloroethyl thiocyanate and 2-chloro*cyclo*hexyl thiocyanate, in 80% yields. The latter compound had previously been prepared [11] by a reaction between *cyclo*hexene, phenyl iododichloride, and lead thiocyanate, in which thiocyanogen chloride may well have been an intermediate, but this preparation was incidental to other work and was not commented upon by the authors. Reaction of thiocyanogen chloride with styrene, *iso*butene, or butadiene yielded mixed products. This could be due to addition in both directions at the unsymmetrically substituted olefinic bonds, as occurs with iodine chloride.[12] There is also the possibility that secondary reactions had occurred or that the addition had given some *iso*thiocyanate, as is known for certain addition reactions between olefins and thiocyanic acid.[13] The rapidity with which thiocyanogen chloride combined with all the

* The addition reaction was observed during the War by one of us (R. G. R. B.) in the Research Laboratories of Imperial Chemical Industries Limited, Dyestuffs Division, whom we thank for permission to refer to the experiments.

[11] Farmer and Shipley, *J.*, 1947, 1519.
[12] Ingold and Smith, *J.*, 1931, 2742, 2752.
[13] Luskin, Gantert, and Craig, *J. Amer. Chem. Soc.*, 1956, **78**, 4965.

XUM

olefins shows it to be a more reactive compound than thiocyanogen, which exhibits negligible reaction unless subjected to ultraviolet irradiation.[14]

By analogy with iodine chloride, thiocyanogen chloride should act as a thiocyanating agent for aromatic compounds:

$$RH + Cl{\cdot}SCN \longrightarrow R{\cdot}SCN + HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Such reactions would involve transfer of all the thiocyanate groups from the reagent to the aromatic molecule, whereas substitutions with thiocyanogen involve transfer of only half the thiocyanate groups:

$$RH + (SCN)_2 \longrightarrow R{\cdot}SCN + HSCN \quad . \quad . \quad . \quad . \quad . \quad (2)$$

We examined the behaviour of *NN*-dimethylaniline, phenol, and anisole; the relative reactivity of these compounds in nuclear substitutions diminishes in the order here given.[15] The reactions were in carbon tetrachloride, which is a poor medium for nuclear substitution, but was chosen for the reason given above.

Whereas Lecher and Joseph's polymeric thiocyanogen chloride attacked dimethylaniline only under drastic conditions, the reaction with our 0·1M-solutions was instantaneous at 0°, and *p*-thiocyanatodimethylaniline was isolated in 75% yield, reckoned on the basis of reaction (1), together with amorphous material. Dimethylaniline is so reactive that even thiocyanogen reacted with it instantaneously under the same conditions, giving the same product in practically quantitative yield, reckoned on the basis of reaction (2). The relative reactivity of Cl·SCN and $(SCN)_2$ towards phenol could be readily distinguished; the former reaction was almost too fast for measurement at 0°, whereas the rate of the latter reaction exhibited the very poor reproducibility which is common for nuclear aromatic halogenations in carbon tetrachloride,[16] but the time required for 50% reaction was of the order of 100—1000 times greater than in the case of thiocyanogen chloride. The same product, *p*-thiocyanatophenol, was obtained, yields of isolated compound being of the order of 75%, reckoned on the basis of reactions (1) and (2) respectively. The gaseous product formed in the reaction with thiocyanogen chloride was hydrogen chloride, and the amount measured was in good agreement with the quantity of *p*-thiocyanatophenol isolated. In the case of anisole, neither thiocyanogen nor thiocyanogen chloride reacted over long periods, while chlorine, under similar conditions, reacted slowly. In none of our experiments with thiocyanogen chloride did we obtain evidence for nuclear chlorination.

From the experiments here reported the conclusions to be drawn are: (*a*) that monomeric thiocyanogen chloride appears to exist in organic solvents and to be polarised in the manner $\overset{\delta-}{Cl}\text{–}\overset{\delta+}{SCN}$; (*b*) that its chemical behaviour is broadly similar to that of the halogens and interhalogen compounds; (*c*) that its degree of reactivity is intermediate between that of thiocyanogen and chlorine and is somewhat comparable with that of iodine chloride; and (*d*) that it is probably not in equilibrium with thiocyanogen and chlorine, in which respect it appears to resemble iodine chloride rather than bromine chloride.

## Experimental

*Thiocyanogen Solutions.*—Standard procedures [2,3] were used for the reaction of bromine with a small excess of lead thiocyanate, at 0°, to produce solutions varying from 0·1 to ~2N-thiocyanogen in chloroform, benzene, toluene, or ethylene dichloride. Thiocyanogen was estimated by adding an aliquot part to excess of 10% methanolic potassium iodide and titrating the liberated iodine with thiosulphate. With dry and purified materials the yields were usually 95—100% (on "AnalaR" bromine). Attempts to prepare ~N-solutions in carbon tetrachloride gave abnormally low conversions and abnormally unstable solutions; the residual

[14] Söderbäck, *Annalen*, 1925, **443**, 142.
[15] Robertson, de la Mare, and Swedlund, *J.*, 1953, 782.
[16] Robertson, de la Mare, and Johnston, *J.*, 1943, 276.

lead salts contained an unstable product (? thiocyanogen) which frequently showed sudden and exothermic decomposition as solvent evaporated. Preparations with light petroleum as solvent showed similar characteristics. 0·1—0·2N-Thiocyanogen in carbon tetrachloride showed very little change in titre over several days at 0°. Typical data for carbon tetrachloride solutions at 20° are:

| Period of storage (hr.): | 0·5 | 1 | 2 | 5 | 20 | 50 |
|---|---|---|---|---|---|---|
| Concentration (N) (i) * ..... | 0·662 | 0·608 | 0·543 | 0·465 | 0·395 | 0·378 |
| (ii) ..... | 0·240 | 0·240 | 0·239 | 0·235 | 0·220 | 0·200 |
| (iii) ..... | 0·0977 | — | — | — | 0·0970 | 0·0936 |

* Initial strength, 0·74N; theoretical value from bromine consumed, 1·05N.

The hygroscopic ammonium, sodium, or potassium thiocyanates (an unconventional choice) could be used, in conjunction with bromine or chlorine, for the preparation of thiocyanogen in hydrocarbons or halogenated hydrocarbons (yields, up to 95% on halogen), provided the salt was thoroughly dried, finely ground, and used in considerable excess.

*Thiocyanogen Chloride Solutions.*—Chlorine was dried with sulphuric acid. For the larger-scale preparations the gas was passed into thiocyanogen solution through a flowmeter until the requisite gain in weight had occurred. For smaller quantities, separate solutions of thiocyanogen and chlorine were mixed in the requisite proportions, iodometric titrations being carried out on the components immediately before mixing and on the product immediately after mixing. Fresh solutions were clear, golden-yellow, and rather pungent. On keeping, their iodometric titre diminished and they slowly became turbid through deposition of amorphous yellow solid.

*2-Chloroethyl Thiocyanate.*—A solution of thiocyanogen (300 ml., 0·67M) in chloroform or toluene was cooled to −60° and 14 g. (0·2 mole) of chlorine were passed in, followed immediately at the same temperature by a stream of ethylene (~0·6 mole). The resulting yellow solution was allowed to attain room temperature and 2 g. of solid were filtered off. Distillation gave 2-chloroethyl thiocyanate (39 g., 80%) as a colourless oil, b. p. 99—100°/20 mm., 198—202°/766 mm. (lit.,[17] 202—203°), $d_4^{23}$ 1·283, $n_D^{23}$ 1·5100; it had an unpleasant, pungent odour and slightly vesicant properties (Found: C, 30·1; H, 3·4; N, 11·4; S, 26·7; Cl, 29·8. Calc. for $C_3H_4NClS$: C, 29·6; H, 3·3; N, 11·5; S, 26·4; Cl, 29·2%). A sample obtained by refluxing ethylene dichloride with ammonium thiocyanate in ethanol (24% yield in 6 hr.) showed b. p. 99—100°/20 mm., $d_4^{23}$ 1·281, $n_D^{23}$ 1·5109.

*2-Chlorocyclohexyl Thiocyanate.*—A solution of thiocyanogen in chloroform or toluene (200 ml., 1·00M) was treated at −60° with chlorine (14 g., 0·2 mole) and then with excess of *cyclo*hexene (0·5 mole), added dropwise. An immediate exothermic reaction occurred, giving a yellow solution, which when distilled yielded 2-chloro*cyclo*hexyl thiocyanate (56 g., 80%), b. p. 154—156°/21 mm., $n_D^{14}$ 1·5308 (Farmer and Shipley [11] give b. p. 90—92°/0·1 mm., $n_D^{15·5}$ 1·5284) (Found: C, 48·1; H, 5·6; N, 7·9; S, 18·6; Cl, 19·9. Calc. for $C_7H_{10}NClS$: C, 47·8; H, 5·7; N, 8·0; S, 18·3; Cl, 20·2%).

*Reaction with Other Olefins.*—Under conditions similar to those described above *iso*butene gave a mixture of liquid fractions (60%), b. p. 60—130°/23 mm., some of which approximated in composition to $C_8H_8NClS$. Styrene gave oils (35%), b. p. 100—180°/30 mm., and much resin. Butadiene gave a mixture of liquid fractions and a viscous residue which decomposed.

*Reactions with Dimethylaniline.*—(*a*) Mixing at 0° of 0·1005M-thiocyanogen in carbon tetrachloride and 0·1044M-chlorine in carbon tetrachloride gave 0·0974M-thiocyanogen chloride (95% of theoretical strength). 720 ml. of this reagent (0·07 mole of Cl·SCN) were treated at 0° with dimethylaniline (8·5 g., 0·07 mole) dissolved in a little carbon tetrachloride; the temperature instantly rose by 10° and yellow solid separated. The precipitate and solution were extracted with excess of 5N-hydrochloric acid, which left some amorphous yellow solid (~1 g.) undissolved. Neutralisation of the acidic extract with ammonia yielded *p*-thiocyanatodimethylaniline (9·4 g., 75%), which crystallised from aqueous methanol in yellow needles, m. p. 72—73°, undepressed by a sample, m. p. 72—73°, prepared by use of ammonium thiocyanate and bromine.[18] (*b*) 0·0973M-Thiocyanogen was prepared in carbon tetrachloride from lead thiocyanate and bromine (97% yield). When dimethylaniline (0·05 mole) was added to 515 ml.

[17] James, *J. pr. Chem.*, 1879, **20**, 351; Josephson, *Biochem. Z.*, 1933, **265**, 448.
[18] "Organic Syntheses," Coll. Vol. 2, p. 574.

XUM

of the solution (0·05 mole of thiocyanogen) at 0°, reaction proceeded as in (*a*). *p*-Thiocyanatodimethylaniline, m. p. 72—73°, was isolated in 95% yield.

*Reactions with Phenol.*—(*a*) Solutions of phenol and of thiocyanogen chloride in carbon tetrachloride were rapidly mixed at 0° to give a solution initially 0·050M in phenol and 0·050M in Cl·SCN. Substitution occurred almost too rapidly for measurement, the temperature rising by 3°; iodometric titration showed reaction to be complete in ~10 min. *p*-Thiocyanatophenol was obtained, partly as a precipitate and partly by evaporation, in 84% yield and had m. p. 52—53° on recrystallisation from water; Söderbäck [2] gives m. p. 53—54°. Similar reactions were effected at 0° and at concentrations of 0·3M, the carbon tetrachloride solution (300 ml.) being swept with dry nitrogen which passed to a 2 ft. glass-packed scrubbing tower where it was in contact with aqueous N-sodium hydroxide. When reaction was over, the temperature was raised to the b. p. and the mixture kept under reflux for a few hours while the nitrogen stream was continued. The collected alkaline wash liquid was analysed volumetrically for chloride, which corresponded with 72—78% of the thiocyanogen chloride employed for the reaction. *p*-Thiocyanatophenol was isolated in an average yield of 73%, together with a little polymer and resin.

(*b*) The rate of reaction between phenol (0·050M) and thiocyanogen (0·050M) at 0° in carbon tetrachloride was followed by iodometric analysis. Rates were fairly slow but were non-reproducible, even in darkness; 2—24 hr. were required for 50% reaction.

(*c*) Under conditions similar to those described in (*a*) and (*b*) above, the reaction of phenol was even faster with chlorine than with thiocyanogen chloride.

*Reactions with Anisole.*—No significant reaction was observed at 0° in a carbon tetrachloride solution 0·1M in anisole and 0·1M in thiocyanogen chloride; the fall in titre of the solution was the same in the absence of anisole as in its presence. Under similar conditions, anisole and chlorine reacted slowly; ~20 hr. were required for 50% reaction.

QUEEN'S UNIVERSITY, BELFAST. [*Received, August 8th*, 1957.]

---

## 151. *Thiocyanogen Chloride. Part II.* Some Physical Properties of its Solutions.*

By R. G. R. BACON and R. S. IRWIN.

Cryoscopic measurements show that thiocyanogen monochloride is essentially monomeric in fresh solutions. In highly polar solvents it exhibits weak electrical conductivity, comparable with that of thiocyanogen, but less than that of iodine chloride. Precipitation reactions with the salt $(Bu^nO)_2PO{\cdot}SNa$ in carbon tetrachloride show that SCN is the more electropositive partner in Cl·SCN, like iodine in iodine monochloride; these reactions involve displacement of the pseudohalogen $[(Bu^nO)_2PO{\cdot}S]_2$, which is more electropositive than thiocyanogen. Compound formation between equimolecular amounts of thiocyanogen and chlorine is proved (as in the case of iodine monochloride) by examination of absorption spectra in the visible and near ultraviolet regions. The known properties of thiocyanogen chloride could be accounted for by a structure polarised $Cl^{\delta-}-S^{\delta+}-C{\equiv}N$, but the infrared absorption spectrum suggests that this does not accurately represent the nature of the bonds in the molecule. All measurements made on thiocyanogen chloride solutions are limited by their instability, which varies with the nature of the solvent and with other factors.

IT was shown in Part I that a rapid chemical change occurs when solutions of thiocyanogen and chlorine are mixed in equimolecular proportion. The mixture behaves as a solution of reactive molecules of formula Cl·SCN, in which the thiocyanate group is the more electropositive partner. As further evidence for the nature of these solutions we now report (*a*) cryoscopic measurements, (*b*) ionic precipitation reactions, (*c*) electrical conductivity measurements, and (*d*) spectroscopic characteristics. Some comparisons have been made

* Part I, preceding paper.

XUM

both with thiocyanogen and with iodine chloride; thiocyanogen chloride somewhat resembles the latter compound in chemical properties.

All measurements on thiocyanogen chloride inevitably lack precision because it cannot be isolated for purification. It is generated in solution and the yield, as measured by iodometric titration, is not quantitative (see Part I); also it decomposes at a rate influenced by the nature and purity of the solvent, and by temperature and light. Suitable solvents are, for example, acetic acid or carbon tetrachloride, in which decomposition is usually not greater than 0·5%/hr. at 20° in 0·1N-solution. Measurements are therefore necessarily made in the presence of varying amounts of contaminants, among which polymers are probably important. When investigating the stability of solutions we paid attention to the effect of hydrogen chloride on decomposition rate, since this compound is produced when thiocyanogen chloride participates in substitution reactions (Part I). In 0·1—0·5N-Cl·SCN in acetic acid at 20°, the presence of an equimolecular quantity of hydrogen chloride had a negligible effect.

*Cryoscopic Measurements.*—Measurements in benzene, acetic acid, and bromoform all indicated that the substance in freshly prepared solutions is essentially monomeric, and not a polymer such as earlier workers described (see Part I). Decomposition rate was higher than usual in the solutions being examined, possibly because of the increase in concentration which accompanies freezing. Mean deviations from the theoretical molecular weight were ~+3%, which, if significant, could be due to a slight degree of polymerisation. The cryoscopic technique was checked with iodine chloride, measurements being made on solutions of the purified solid and also on solutions prepared, analogously to thiocyanogen chloride, by mixing iodine and chlorine.[1] The measurements in bromoform were similar in principle to those of Lecher and Goebel,[2] who showed that the freezing-point depression due to $Br_2$ molecules in this solvent was not changed when they were replaced by $(SCN)_2$ molecules through reaction with a suspension of lead thiocyanate: $Pb(SCN)_2 + Br_2 \longrightarrow PbBr_2 + (SCN)_2$. In the present case the depression due to chlorine was not altered by stirring with a 0·5 molar proportion of lead thiocyanate, the reaction occurring being:[3] $Pb(SCN)_2 + 2Cl_2 \longrightarrow PbCl_2 + 2Cl{\cdot}SCN$. Because of its reactivity this solvent is by no means an ideal choice.

*Ionic Precipitation Reactions.*—Reactions were examined for evidence of the polarisation $\overset{\delta+}{SCN}\text{–}\overset{\delta-}{Cl}$ which had been indicated by the mode of substitution in aromatic compounds (Part I). Like iodine chloride, thiocyanogen chloride gave an immediate precipitate with silver perchlorate in organic solvents, but more attention was given to reactions with sodium *OO*-dialkyl thiophosphates. These compounds[4] have the unusual property of very high solubility in water coupled with substantial solubility in organic solvents, including hydrocarbons and chlorinated hydrocarbons. We found that the di-*n*-butyl compound had particularly good solubility in organic solvents. It appeared to be completely dissociated in aqueous solution and to be associated about ten-fold in benzene.

Dissolved in carbon tetrachloride with an equimolecular proportion of thiocyanogen chloride, the salt gave a precipitate of sodium chloride, free from thiocyanate, in 90% yield. This is due to the reaction:

$$2(Bu^nO)_2PO{\cdot}SNa + 2Cl{\cdot}SCN \longrightarrow 2NaCl + (SCN)_2 + [(Bu^nO)_2PO{\cdot}S]_2 \quad . \quad (1)$$

which may be linked with:

$$(SCN)_2 + [(Bu^nO)_2PO{\cdot}S]_2 \rightleftharpoons 2(Bu^nO)_2PO{\cdot}S{\cdot}SCN \quad . \quad . \quad . \quad (2)$$

In the same solvent, with a 2 : 1 thiophosphate : Cl·SCN ratio, the precipitated salt

[1] Gillam and Morton, *Proc. Roy. Soc.*, 1929, *A*, **124**, 604.
[2] Lecher and Goebel, *Ber.*, 1921, **54**, 2223.
[3] Bacon and Guy, unpublished data.
[4] Foss, *Acta Chem. Scand.*, 1947, **1**, 8.

consisted of equal proportions of sodium chloride and sodium thiocyanate. The latter can be attributed to a reaction (3) occurring in conjunction with (1):

$$2(Bu^nO)_2PO{\cdot}SNa + (SCN)_2 \longrightarrow 2NaSCN + [(Bu^nO)_2PO{\cdot}S]_2 \quad . \quad . \quad (3)$$

We demonstrated reaction (3) by mixing the thiophosphate with thiocyanogen in carbon tetrachloride, whereupon sodium thiocyanate was precipitated quantitatively. We also carried out a reaction analogous to (1), but using iodine chloride, and a quantitative precipitation of sodium chloride occurred:

$$2(Bu^nO)_2PO{\cdot}SNa + 2ICl \longrightarrow 2NaCl + I_2 + [(Bu^nO)_2PO{\cdot}S]_2 \quad . \quad . \quad (4)$$

The phosphorus compound produced in reactions (1), (3), and (4) is one of the group called by Foss [4] dialkylthiophosphatogens. He prepared the dimethyl and diethyl compounds with the aid of bromine in ether and we used his method to isolate a sample of the di-*n*-butyl compound:

$$2(Bu^nO)_2PO{\cdot}SNa + Br_2 \longrightarrow 2NaBr + [(Bu^nO)_2PO{\cdot}S]_2$$

This was an oil, unstable to heat, like its homologues. Reaction (3) has a formal similarity (involving disulphide-bond fission) with the double-decomposition process in aqueous solution which Foss [4] used to prepare the higher dialkylthiophosphatogens from the water-soluble dimethyl compound:

$$2(RO)_2PO{\cdot}S^- + [(MeO)_2PO{\cdot}S]_2 \longrightarrow 2(MeO)_2PO{\cdot}S^- + [(RO)_2PO{\cdot}S]_2 \text{ (precipitated)}$$

Reaction (1) demonstrates that the SCN group is the more electropositive partner in the compound Cl·SCN, just as iodine is in ICl [reaction(4)]. Also, the experiments provide new examples of displacement reactions between pseudohalogens, *i.e.*, displacement of $(RO)_2PO{\cdot}S$ from its salts by the more electronegative SCN group. Foss [4] found the redox potential for the system $2(Bu^nO)_2PO{\cdot}S^- \longrightarrow [(Bu^nO)_2PO{\cdot}S]_2 + 2e$ to be $-0{\cdot}51$, which is close to the value for $I{-}I^-$ ($-0{\cdot}54$), whereas the value for $SCN{-}SCN^-$ has been found [5] to be $-0{\cdot}77$. The suggested reaction (2) between the two pseudohalogens would be analogous to those which occur between pairs of halogens, or between a halogen and a pseudohalogen.

*Electrical Conductivity.*—Iodine chloride conducts in polar solvents and precise data have been obtained [6] for its conductivity in the molten state, which is probably due to the self-ionisation $2ICl \longrightarrow I^+ + ICl_2^-$. Thiocyanogen has been found to be non-conducting in halogenated hydrocarbons, ether, and carbon disulphide and to display weak conductivity in mixtures of ethyl bromide and acetone.[7] We found thiocyanogen chloride to be non-conducting in carbon tetrachloride, chloroform, and benzene, and we compared it with iodine chloride and with thiocyanogen in solvents of higher dielectric constant. Typical data are shown in the Table. No great accuracy can be claimed since

*Molar conductance (ohm$^{-1}$ cm.$^2$) of solutions at 25°.*

| | $(SCN)_2$ | | Cl·SCN | | ICl | |
|---|---|---|---|---|---|---|
| Solvent | 0·08M | 0·008M | 0·08M | 0·008M | 0·08M | 0·008M |
| Acetic acid ($\varepsilon = 7$) ..... | slight | slight | slight | slight | $4 \times 10^{-4}$ | $3 \times 10^{-4}$ |
| Acetic anhydride ($\varepsilon = 20$) | $1{\cdot}4 \times 10^{-2}$ | $2{\cdot}1 \times 10^{-2}$ | $0{\cdot}9 \times 10^{-2}$ | $3{\cdot}1 \times 10^{-2}$ | $12 \times 10^{-2}$ | $35 \times 10^{-2}$ |
| Nitromethane ($\varepsilon = 39$)... | $3{\cdot}7 \times 10^{-2}$ | $7 \times 10^{-2}$ | $0{\cdot}5 \times 10^{-2}$ | — | 1·5 | 2·5 |

chemical reactions occurred quite readily in the case of iodine chloride in acetic anhydride and thiocyanogen chloride in nitromethane; their effect was minimised by taking rapid readings on fresh solutions. The data show the molar conductance of thiocyanogen

[4] Bjerrum and Kirschner, *Kgl. Danske Videnskab. Selsk.*, 1918, **5**, No. 1.
[6] Greenwood and Emeléus, *J.*, 1950, 987.
[7] Fialkov and Kleiner, *J. Gen. Chem., U.S.S.R.*, 1941, **11**, 671.

chloride to be of the same order as that of thiocyanogen and to be lower than that of iodine chloride by a factor of 10—100.

*Spectroscopic Characteristics.*—When solutions of thiocyanogen and chlorine are mixed, their colours, very pale yellow and green-yellow respectively, are replaced by the intenser golden-yellow of thiocyanogen chloride solution. Analogous interactions between chlorine, bromine, and iodine were investigated in carbon tetrachloride by Gillam and Morton,[1] with the aid of absorption spectra in the visible and near-ultraviolet regions. We used

FIG. 1. *Spectra in carbon tetrachloride at room temperature. A,* 0·0129M-Cl·SCN; *B, theoretical curve for a* 0·0129M-*solution containing a non-reacted equimolecular mixture of* $(SCN)_2$ *and* $Cl_2$; *C, due to* 0·00645M-$(SCN)_2$, *and D, due to* 0·00645M-$Cl_2$, *are added to give B.*

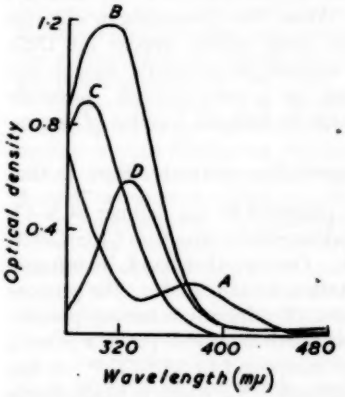
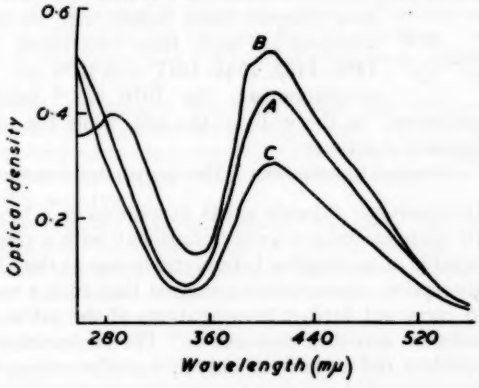



FIG. 2. *Spectra in carbon tetrachloride at room temperature. A, observed curve for a* 0·00517M-*solution, made from an equimolecular mixture of* $(SCN)_2$ *and* $Br_2$; *B, theoretical curve for solution A if no reaction has occurred,* i.e., *summation of curves for* 0·00259M-$(SCN)_2$ *and* 0·00259M-$Br_2$; *C, solution A after* 100 *hr. in the dark at room temperature.*




the same method in the present case and observed a similar result (Fig. 1) to that reported by Gillam and Morton for the formation of iodine chloride. The peaks characteristic of chlorine ($\lambda_{max.}$ 327 mμ, $\varepsilon_{max.}$ 90) and of thiocyanogen ($\lambda_{max.}$ 295 mμ, $\varepsilon_{max.}$ 140) were completely absent from the absorption spectrum of the mixture in carbon tetrachloride, which we regard as characteristic of thiocyanogen chloride ($\lambda_{max.}$ 372 mμ, $\varepsilon_{max.}$ ~15; $\lambda_{min.}$ 338 mμ, $\varepsilon_{min.}$ ~10). In acetic anhydride the curve was similar, but with a peak at slightly shorter wavelength ($\lambda_{max.}$ 366 mμ), while the curve in *n*-hexane was practically identical with that in carbon tetrachloride ($\lambda_{max.}$ 375 mμ); the rise in the curve continued down to 225 mμ.

By contrast (Fig. 2) the absorption spectrum (*A*) for a mixture of bromine and thiocyanogen in carbon tetrachloride approached much more closely to the summation curve (*B*) for the two components. In the mixture (*A*) the bromine peak at 411 mμ was somewhat less intense than in (*B*) and there was a considerable fall from this initial intensity when the mixture was kept, indicating some kind of chemical change. The thiocyanogen peak was not present at 295 mμ in (*A*), but absorption was displaced to shorter wavelengths, beyond the range which could be examined in this solvent. Further investigation is needed to determine whether these effects can be attributed to an equilibrium such as $Br_2 + (SCN)_2 \rightleftharpoons 2BrSCN$. No chemical evidence has yet been reported for the existence of thiocyanogen bromide in solution, though a compound believed to be BrSCN has been isolated at −50° as a readily dissociating red solid.[8]

A preliminary investigation of infrared absorption spectra showed the need of great caution in interpreting results, since observed bands may be due to impurities, or to polymers and other decomposition products. Solutions of thiocyanogen of reasonable

[8] Seel and Müller, *Chem. Ber.*, 1955, **88**, 1747.

concentration may be prepared in purified (ethanol-free) chloroform. A 0·48M-solution in this solvent showed bands at 3050 (m) and 2175 cm.$^{-1}$ (m) (in the range 800—4000 cm.$^{-1}$). Thiocyanogen chloride (initially 0·43M) showed the following characteristics in the same solvent (1200—1250 cm.$^{-1}$ region uncertain because of high absorption by chloroform):

| Frequency (cm.$^{-1}$) | 3050 | 2170 | 1595 | 1453 | 1345 | 930 * | 912 * |
|---|---|---|---|---|---|---|---|
| Freshly prepared solution | w | w | s | — | vw | — | ms |
| After 24 hr. (33% decomposition) | w | w | s | ms | ms | vs | m |
| After 296 hr. (100% decomposition) | vw | vw | — | vs | s | — | — |

* Complex group of bands; rate of replacement of the 912 cm.$^{-1}$ band was not reproducible.

Organic thiocyanates and *iso*thiocyanates are respectively characterised [9] by a strong peak at 2130—2160 cm.$^{-1}$ and a strong band at 2040—2180 cm.$^{-1}$. The frequency in this region is very weak in Cl·SCN and only moderate in $(SCN)_2$. Strong peaks observed at 1600 and ~930 cm.$^{-1}$ in the Cl·SCN spectrum are also found in the spectra of the trichloride $Cl{\cdot}S{\cdot}CNCl_2$ and its derivatives [10] and have been attributed, respectively, to a C : N link and to a chlorine atom linked, *e.g.*, as in (I). When the thiocyanogen chloride solutions are kept, these two bands diminish, while others appear (at 1527, 1482, 1453, 1345, 1317, and 1070 cm.$^{-1}$) and increase in intensity, though not synchronously; the 1070 cm.$^{-1}$ band is due to a solid deposit, probably polymeric, on the walls of the cell, while the others seem to indicate a series of decomposition reactions.

(I)

*General Conclusions.*—The properties examined support the postulate (Part I) that thiocyanogen chloride exists in solution as a monomer, polarised in the manner $\overset{\delta+}{S}CN–\overset{\delta-}{Cl}$. Its chemical behaviour is in harmony with a classical valence-bond structure Cl–S–C≡N, capable of undergoing heterolytic fission at the Cl–S link. On the other hand, its infrared absorption characteristics suggest that such a representation is inadequate. We propose to carry out further investigations of the infrared spectra of sulphur-containing pseudohalogens and their derivatives. The formulation of their bonds may well prove a general problem and we have already met another example in the compound $Cl{\cdot}S{\cdot}CNCl_2$.[10] A less closely related case [11] is the unstable, polymerisable compound $S_2N_2$, which is isoelectronic with Cl·SCN.

## Experimental

*Thiocyanogen Chloride Solutions.*—The usual precautions were taken to dry reagents, solvents, and glassware thoroughly. Lead thiocyanate was prepared from " AnalaR " lead nitrate and ammonium thiocyanate by the procedure recommended by Lambou and Dollear [12] and was stirred in the solvent with " AnalaR " bromine. The resulting thiocyanogen solution was displaced from the reaction flask through a sintered-glass plate into a volumetric flask, and washings from the residual salts were displaced similarly. Thiocyanogen chloride was generated in a thiocyanogen solution by adding a calculated quantity of chlorine solution. The latter was made by passing the gas from a cylinder through scrubbing towers containing concentrated sulphuric acid and absorbing it in dry solvent. Solutions of chlorine, thiocyanogen and thiocyanogen chloride were stored in the dark and were estimated by reaction with excess of methanolic potassium iodide, followed by iodometric titration. Thiocyanogen chloride was commonly used in ~0·1N(~0·05M)-solution.

Solutions in acetic anhydride showed ~2% decomposition (by titration) in 20 hr. at 20°. Solutions in carbon tetrachloride or in acetic acid (the latter solvent having been previously refluxed with 5% acetic anhydride) showed ~10% decomposition in 20 hr. at 20°. Solutions in *n*-hexane or benzene were considerably less stable. Solutions in nitromethane had poor stability (~10% decomposition in 1 hr.). In all solvents except acetic anhydride the initial titre for the thiocyanogen chloride was less, by 2—7%, than the figure to be expected from the titre of its components.

The effect of dry hydrogen chloride on the stability of the reagent in solution in acetic acid

[9] Luskin, Gantert, and Craig, *J. Amer. Chem. Soc.*, 1956, **78**, 4965; Bacon and Guy, unpublished data.
[10] Bacon, Irwin, Pollock, and Pullin, *J.*, 1958, 764.
[11] Goehring, *Quart. Reviews*, 1956, **10**, 437.
[12] Lambou and Dollear, *Oil and Soap*, 1946, **23**, 97.

(treated as above) was determined by iodometric titration. The following are typical decomposition rates (%/hr.) observed 1—20 hr. after mixing, at 20° in darkness: 0·1N-Cl·SCN, 0·4; 0·1N-Cl·SCN + 0·1N-HCl, 0·3; 0·3N-Cl·SCN, 0·2; 0·3N-Cl·SCN + 0·3N-HCl, 0·3; 0·5N-Cl·SCN, 0·5; 0·5N-Cl·SCN + 0·5N-HCl, 0·8.

*Cryoscopic Measurements.*—(a) *In benzene.* To avoid inconsistencies caused by absorption of water, f. p. determinations were carried out in presence of phosphoric oxide (~0·5%), as recommended by Roberts and Bury.[13] Titrations showed that the presence of this compound improved the stability of thiocyanogen chloride in benzene at 20°. In the time needed for freezing and melting operations (~30 min.) there was an average decline of 5% in the strength of 0·1N-solutions. A normal Beckmann-type apparatus was used with platinum stirrer, mechanically maintained in slow motion. Some precautions recommended by Thompson and Ubbelohde [14] were used in handling the thermometer. Light was excluded from the apparatus. The benzene was purified by refluxing with phosphoric oxide and distillation, and its f. p. determined on the same sample as that used for the reagent. Solutions of thiocyanogen and chlorine were prepared, titrated, and mixed, and the mixture titrated immediately before f. p. determinations. The initial titre of the mixture was used in the molecular-weight calculation. Molecular-weight values were mainly between 96 and 98 and averaged 96·7 (theory 93·5). To check the accuracy of the method, exactly the same procedure was used on mixtures of chlorine and iodine (Found: *M*, 163—165. Calc. for ICl: *M*, 162·4).

(b) *In acetic acid.* The procedure described for benzene was used, except that moisture was excluded by passage of a slow current of dry nitrogen through the apparatus. The average decline in titre during the freezing and melting operations was 6%. The molecular-weight values showed a wider scatter than in benzene but averaged 95. The average found with a purified commercial sample of iodine chloride was 167.

(c) *In bromoform.* A procedure similar to that of Lecher and Goebel [2] was used. Purified bromoform is unstable. Chlorine was passed into the solvent to give a solution showing f. p. depression of 0·532° under dry nitrogen. Lead thiocyanate was added in an amount calculated to give a $Pb(SCN)_2 : Cl_2$ ratio of 1 : 2, and the mixture stirred to effect reaction. The f. p. depression was then 0·507° (5% below its initial value).

*Reactions involving* OO-*Di*-n-*butyl Thiophosphate.*—(i) The salt was prepared by Foss's general procedure [4] for the potassium salt. The sodium salt crystallised from light petroleum (b. p. 60—80°) in hygroscopic needles. It showed infrared absorption bands (5% chloroform solution) at 3337 (w), 2961 (w), 1466 (w), 1381 (w), 1220 (w), 1133 (vs), 1066 (s), 1024 (s), 1000 (s), 973 (s), 889 (s), and 818 $cm.^{-1}$ (s). Depression of f. p. in 3% aqueous solution indicated complete dissociation. Depression of f. p. in 3% benzene solution indicated ~ten-fold association (Found: *M*, 2370 ± 100).

(ii) A solution of the salt (0·02 mole) in anhydrous ether (100 ml.) was treated with bromine (0·01 mole) in anhydrous ether (100 ml.). The precipitated sodium bromide was filtered off and the colourless filtrate was washed with water and dried, and the solvent evaporated, leaving *bis*-(OO-*di*-n-*butylthiophosphatogen*) [*bisdi*-n-*butoxyphosphinyl disulphide*] as a very pale yellow oil which could not be distilled without decomposition (Found: C, 42·8; H, 7·7. $C_{16}H_{36}O_6S_2P_2$ requires C, 42·7; H, 8·0%); ultraviolet absorption max. (0·007M-$CCl_4$ solution) was 266 mμ (log ε 2·09). Reaction was also carried out with a mixture prepared in carbon tetrachloride, 0·022M in $(SCN)_2$ and 0·044M in $(Bu^nO)_2PO{\cdot}SNa$. Sodium thiocyanate was immediately precipitated (99% of theoretical amount) and the filtrate showed the same ultraviolet characteristics as the above sample ($\lambda_{max.}$ 264 mμ, log ε 2·13).

(iii) A mixture was prepared in carbon tetrachloride, 0·0484M in Cl·SCN and 0·0968M in $(Bu^nO)_2PO{\cdot}SNa$. The colour immediately faded. The finely divided salt which immediately separated was extracted into water and recovered by evaporation. Analysis by a standard procedure [15] showed NaCl, 50·4; NaSCN, 49·6%; the total weight of precipitate was 99% of the theoretical for a mixture of this composition.

(iv) A mixture was prepared in carbon tetrachloride, 0·0488M in Cl·SCN and 0·0488M in $(Bu^nO)_2PO{\cdot}SNa$. The salt, which immediately appeared as a finely divided precipitate, was isolated by filtration and found to be exclusively sodium chloride (yield, 90% of the theoretical).

[13] Roberts and Bury, *J.*, 1923, 2037.
[14] Thompson and Ubbelohde, *Trans. Faraday Soc.*, 1950, **46**, 349.
[15] Kolthoff and Stenger, "Volumetric Analysis," Vol. 2, Interscience, New York, 1947, pp. 266—268.

XUM

(v) A mixture was prepared in carbon tetrachloride, 0·0472M in ICl and 0·0472M in $(Bu^nO)_3PO{\cdot}SNa$. The colour changed from brown to the red-brown of iodine. Salt was immediately precipitated and when isolated by filtration was found to be exclusively sodium chloride (yield, 97% of the theoretical).

*Conductivity Measurements.*—A standard type of conductivity cell and bridge assembly was used (limit of measurement: specific conductance $\leqslant 1 \times 10^{-7}$ ohm$^{-1}$ cm.$^{-1}$). In "AnalaR" acetic anhydride, 0·05M-thiocyanogen showed excellent stability at 20° (no change during 3 hr., then decomposition at ~0·04%/hr.). The stability of 0·12M-thiocyanogen chloride was also good in this solvent at 20° (no change during 2 hr., then decomposition at ~0·15%/hr.). A fairly fast reaction occurred with iodine chloride and acetic anhydride, leading to a moderate increase in conductivity (max. after ~10 min. at 0·25M) followed by a fall to zero (~100 min.). In purified nitromethane the stability of 0·1M-thiocyanogen was good (0·25% decomposition/hr.), but the stability of thiocyanogen chloride was poor (decomposition ~10%/hr.); no reaction was noticed with iodine chloride. In the cases where reaction with solvent intruded, the effect was minimised by taking readings as quickly as possible after the preparation of solutions.

*Spectroscopic Data.*—Absorptions in the visible and near ultraviolet regions were recorded on a Unicam S.P. 500 spectrophotometer at room temperature, using a quartz cell of 1 cm. light path. Infrared spectra were recorded on a Perkin-Elmer Model 21 Spectrophotometer.

We thank the Shell Petroleum Company Ltd. for financial assistance (to R. S. I.), and Dr. A. D. E. Pullin for his help in the interpretation of infrared spectroscopic data.

QUEEN'S UNIVERSITY, BELFAST. [*Received, August 8th*, 1957.]

---

## 152. *An Infrared Spectroscopic Examination of Some Anhydrous Sodium Soaps.*

By D. CHAPMAN.

The infrared spectra of a series of sodium soaps have been obtained in the range 1800—650 cm.$^{-1}$ and various features of the spectra from acetate to stearate are discussed. The effect of heat on anhydrous sodium stearate and palmitate has been investigated. The liquid-crystalline form of these soaps is discussed.

CHILDERS and STRUTHERS [1] showed that the infrared spectra of the sodium soaps from the acetate to the hexanoate are useful in characterising the corresponding fatty acids. Recently, Meikeljohn *et al.*[2] extended this work, using barium soaps up to $C_{36}$, and point out an empirical relationship between the number of bands in the 1250 cm.$^{-1}$ region and the number of carbon atoms in the chain.

### EXPERIMENTAL

The sodium soaps from $C_8$ to $C_{18}$ were prepared by standard methods from aqueous sodium hydroxide and an ethanolic solution of the acid; the acids were very pure. The even-numbered acids were presented by Dr. S. Paul, and the odd-numbered acids by Dr. J. Devine, of these laboratories. The soaps of fatty acids of shorter chain-length were similarly prepared from commercial acids of B.D.H. quality.* To obtain the anhydrous forms, each soap was heated to 140° in a vacuum oven for several hours in the presence of phosphoric oxide. All spectra shown were obtained by means of potassium chloride discs (several additional spectra were obtained with Nujol mulls).

A Grubb-Parsons S.3 double-beam infrared spectrometer was used, with a heated cell for the investigation of the effects of temperature on the anhydrous soaps.

* The physical characteristics of most of the acids used have been previously described.[11] The setting points or m. p.s of the remaining acids are as follows: $C_{13}$, m. p. 41—41·5°; $C_{14}$, s. p. 53·9°; $C_{16}$, s. p. 62·25°; $C_{17}$, m. p. 57·5—58°; $C_{18}$, s. p. 69·3°.

[1] Childers and Struthers, *Analyt. Chem.*, 1955, **27**, 737.
[2] Meikeljohn, Meyer, Aronovic, Schuette, and Meloche, *ibid.*, 1957, **29**, 329.

## Results and Discussion.

The spectra of the anhydrous sodium soaps are shown in Figs. 1 and 2 over the range 1800—650 cm.$^{-1}$. For a detailed analysis of the spectra we can first consider the bands which arise from vibrations of the carboxylate group and then those of the paraffinic chain.

In relation to the bands arising from vibrations of the carboxylate group Lecomte and his co-workers [3] have shown that when ionisation occurs giving rise to the CO·O$^-$ group, resonance is possible between the two C–O bonds, and that the usual carbonyl absorption vanishes and is replaced by two bands, approximately between 1610 and 1550 cm.$^{-1}$ and between 1400 and 1300 cm.$^{-1}$. These bands correspond to the antisymmetrical and symmetrical vibrations of the CO·O$^-$ structure.

Ito and Bernstein,[4] dealing with the spectrum of solid sodium acetate, assigned bands at 1578 cm.$^{-1}$ and 1414 cm.$^{-1}$ to C–O stretching vibrations and a band at 646 cm.$^{-1}$ to a CO·O$^-$ deformation frequency. The spectra of all the anhydrous sodium soaps examined here exhibit bands near 1560 and 1415, and at 695 cm.$^{-1}$, which can be similarly assigned. (Both the acetate and the propionate have the last band at a lower frequency, but the band remains constant in frequency with further increase of chain length.)

A fairly complete assignment of long-chain paraffins is now available [5] and this enables us to discuss the remaining bands in the spectra of the sodium soaps.

Two constant sets of bands at 1460 and 1380 cm.$^{-1}$ are observed in all the spectra; they arise from $CH_2$ and $CH_3$ symmetrical bending deformation modes. These frequencies are well known and are observed in the infrared spectra of all long-chain compounds. The relative intensity of the 1380 cm.$^{-1}$ band decreases as the length of chain increases. A band at 1440 cm.$^{-1}$ may be tentatively assigned to the vibration of the $CH_2$ group adjacent to the carboxylate group by analogy with a similar assignment in carboxylic acids.[6] A very prominent feature of the spectra of the soaps is a set of absorption bands marked by the intensity and regularity of its members in the 1200—1350 cm.$^{-1}$ region. Analogous regular series of bands have been observed in this region of the spectrum of many long-chain compounds including paraffins,[5] bromides,[7] fatty acids,[8] and glycerides.[9] In the alkyl bromides Brown and Sheppard [7] have shown clearly that the bands arise from $CH_2$ wagging modes and originate near 1250 cm.$^{-1}$. In the monocarboxylic acids Jones *et al.*[8] assign the bands generally to $CH_2$ wagging and twisting modes. Meikeljohn *et al.*[2] noted a similar series in the spectra of some barium soaps and point out an empirical relationship between the number of bands and the number of carbon atoms in the chain. (The number of bands for even numbers of carbon atoms is equal to half the number of carbon atoms, whilst for odd numbers of carbon atoms it is half the number of carbon atoms + 1.) Certain anomalies to this relationship were observed for the soaps below $C_{16}$ owing to weaker intermediate bands which had to be disregarded. Our spectra of the anhydrous sodium soaps show no such anomalies and the empirical rule rigidly holds.

The distribution clearly originates in the spectrum of sodium propionate near 1300 cm.$^{-1}$. One would expect the number of bands observed to be related to the number of methylene groups present rather than to the total number of carbon atoms; *e.g.*, Brown *et al.*[5] discussed the selection rules for methylene wagging modes for odd-numbered hydrocarbons and stated that one band should be observed for every methylene group. With the anhydrous sodium soaps this is true, however, for only the first few members (Table 1).

[3] Duval, Lecomte, and Douville, *Ann. Phys.*, 1942, **17**, 5; *Bull. Soc. chim. France*, 1942, **9**, 263.
[4] Ito and Bernstein, *Canad. J. Chem.*, 1956, **34**, 170.
[5] Brown, Sheppard, and Simpson, *Phil. Trans.*, 1954, *A*, **247**, 35.
[6] Francis, *J. Chem. Phys.*, 1951, **19**, 942.
[7] Brown and Sheppard, *Trans. Faraday Soc.*, 1954, **50**, 535.
[8] Jones, McKay, and Sinclair, *J. Amer. Chem. Soc.*, 1952, **74**, 2575; Von Sydow, *Acta Chem. Scand.*, 1955, **9**, 1119.
[9] Chapman, *J.*, 1956, 2522.

The distribution is very similar to that for *n*-alkyl bromides.[7] In terms of the methylene groups the number of bands for the even-numbered soaps is $\frac{1}{2}n + 1$ and for odd-numbered, excluding sodium propionate $\frac{1}{2}(n + 1) + 1$ (where $n$ is the number of methylene groups). An interesting feature of the distribution is that for the odd-numbered soaps the highest-frequency band is always at a higher frequency than that of the even-numbered soaps, *i.e.*, the frequency of the band alternates from even- to odd-numbered soap; furthermore, whilst the same number of bands are observed in the spectra of an odd-numbered soap as in the spectra of the next higher even-numbered soap, yet all the bands are shifted in frequency. This could be useful in distinguishing odd- and even-numbered soaps.

FIG. 1. *Infrared spectra of anhydrous sodium soaps (acetate to octanoate).*

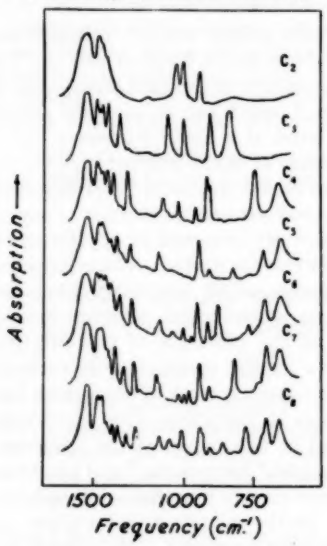
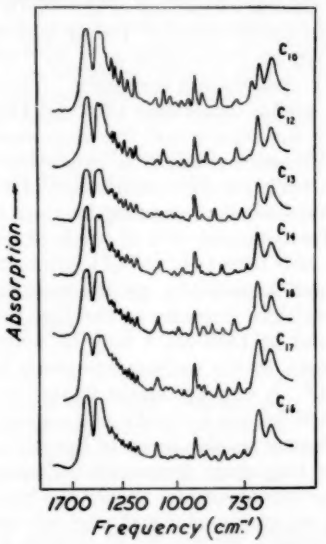



FIG. 2. *Infrared spectra of anhydrous sodium soaps (decanoate to stearate).*




The frequency difference between the highest-frequency band and the next band of lower frequency is always less than the frequency difference between the other bands. This was also observed with the barium soaps [2] and related tentatively to the presence of the α-methylene group. (The C–H distances in this group are probably greater than in the other methylene groups.) The high-frequency band, in contradistinction to the other bands in the distribution, which tend to spread out in frequency, moves gradually to lower frequencies as the chain length increases.

In the spectrum of sodium oleate, there are only five bands in this region and the

TABLE 1.

| No. of C atoms in soap | No. of $CH_2$ groups | No. of bands observed in 1250 cm.$^{-1}$ region | Diff. between cols. 2 and 3 | No. of C atoms in soap | No. of $CH_2$ groups | No. of bands observed in 1250 cm.$^{-1}$ region | Diff. between cols. 2 and 3 |
|---|---|---|---|---|---|---|---|
| 3 | 1 | 1 | 0 | 11 * | 9 | 6 | 3 |
| 4 | 2 | 2 | 0 | 12 | 10 | 6 | 4 |
| 5 | 3 | 3 | 0 | 13 | 11 | 7 | 4 |
| 6 | 4 | 3 | 1 | 14 | 12 | 7 | 5 |
| 7 | 5 | 4 | 1 | 15 * | 13 | 8 | 5 |
| 8 | 6 | 4 | 2 | 16 | 14 | 8 | 6 |
| 9 * | 7 | 5 | 2 | 17 | 15 | 9 | 6 |
| 10 | 8 | 5 | 3 | 18 | 16 | 9 | 7 |

* It is assumed that the empirical rule observed with the other soaps also holds for these soaps.

empirical rule-of-two relationship is apparently not obeyed. This is to be expected, however, owing to the introduction of a double bond in the chain. There are nine carbon atoms on each side of the double bond (or seven methylene groups). In this case therefore each of the chains on either side of the double bond appears to vibrate separately, and to obey the empirical rule individually.

Two marked series of absorption frequencies can be traced in the spectra, one of which extends from 1075 cm.$^{-1}$ in the spectrum of sodium propionate (1042 cm.$^{-1}$ in sodium acetate) to 1105 cm.$^{-1}$ in that of sodium stearate, and the other which extends from 990 cm.$^{-1}$ in the spectrum of sodium propionate (1009 cm.$^{-1}$ in sodium acetate) to 920 cm.$^{-1}$ in that of sodium stearate. These series are analogous to those observed in the spectra of crystalline paraffins and alkyl bromides and can be broadly assigned to methyl rocking modes. (They are also consistent with the previous assignments of the bands in this region in the spectrum of sodium acetate.[4]) These assignments receive additional confirmation from the fact that in the spectra of the liquid-crystalline form (see Fig. 3) these bands are the least affected by this change of state. This is to be expected for these modes: the skeletal frequencies will be more likely to be affected by such a change. Bands occurring between 1080 and 940 cm.$^{-1}$ probably arise from C–C skeletal vibrations.

A series of bands in the 900—720 cm.$^{-1}$ region are attributed to $CH_2$ rocking modes. The most characteristic series of bands in this region are listed in Table 2, which also lists the corresponding $CH_2$ rocking frequencies for the normal paraffins [10] and monocarboxylic acids.[11]

The general similarity of these frequencies in the spectra of the soaps with those of the paraffins (and monocarboxylic acids) suggests that the chains at room temperature are predominantly in the planar *trans*-zigzag configuration similar to the chains in paraffins in the crystalline state.[10]

An important feature about the main $CH_2$ rocking vibration in the spectra, *e.g.*, of sodium stearate or palmitate, is that this band is single. Many long-chain compounds however show a doublet in this region. Chapman [12] has suggested that the presence of a doublet is indicative of orthorhombic packed hydrocarbon chains, whilst a single band in this region is indicative of triclinic packed chains, so we may deduce that the hydrocarbon chains of the sodium soaps are probably triclinically packed, as observed with silver stearate. [3]

TABLE 2.

| | Paraffins | Mono-carboxylic acids | Sodium soaps | | Paraffins | Mono-carboxylic acids | Sodium soaps |
|---|---|---|---|---|---|---|---|
| $n$ | $H\cdot[CH_2]_n\cdot H$ | $H\cdot[CH_2]_n\cdot CO_2H$ | $H\cdot[CH_2]_n\cdot CO_2Na$ | $n$ | $H\cdot[CH_2]_n\cdot H$ | $H\cdot[CH_2]_n\cdot CO_2H$ | $H\cdot[CH_2]_n\cdot CO_2Na$ |
| 2 | 822 | 807 | 812 | 6 | 726 | 724 | 723 |
| 3 | 748 | 750 | 748 | 7 | 723 | 723 | 721 |
| 4 | 732 | 731 | 728 | 8 | 722 | 723 | 720 |
| 5 | 728 | 727 | 726 | 9 | 720 | 721 | 719 |

Several other series can be traced in this region but they are not quite so marked as those which occur in the infrared spectra of the crystalline paraffins. One series starts at 850 cm.$^{-1}$ in sodium hexanoate and reaches a limit near 720 cm.$^{-1}$ in sodium laurate.

*Effect of Heat on the Anhydrous Soaps.*—Several changes of state occur when an anhydrous sodium soap is heated from room temperature to the m. p.;[14-18] *e.g.*, dilatometric measurements [17] over this temperature range show two gross irregularities in the

[10] Brown, Sheppard, and Simpson, *Discuss. Faraday Soc.*, 1950, **9**, 261.
[11] Corish and Chapman, *J.*, 1957, 1746.
[12] Chapman, Sixth Internat. Spectroscopic Colloquium Symp., Amsterdam, 1956.
[13] Vand, Aitken, and Campbell, *Acta Cryst.*, 1949, **2**, 398.
[14] Vold, Rosevear, and Ferguson, *Oil and Soap*, 1939, **16**, 48.
[15] Vold and Vold, *J. Amer. Chem. Soc.*, 1939, **61**, 808.
[16] Nordsieck, Rosevear, and Ferguson, *J. Chem. Phys.*, 1948, **16**, 175.
[17] Vold, Macomber, and Vold, *J. Amer. Chem. Soc.*, 1941, **63**, 168.
[18] Southam and Puddington, *Canad. J. Res.*, 1947, **25**, 125.

density–temperature curve at about 105—120° and 200°, with minor breaks at other temperatures. With anhydrous sodium palmitate, five phase transitions [15,17] have been observed between the crystalline state and the isotropic melt. An *X*-ray examination of this soap,[16] however, suggests that these phases can be grouped into two basic structures, named the waxy and neat phase, both being thought to be liquid-crystalline.

The infrared spectra of sodium palmitate at different temperatures are shown in Fig. 3. As the temperature approaches 100° the distribution of bands in the 1250 cm.$^{-1}$ region become less well-resolved, particularly the bands at the high-frequency end of the distribution. This is interpreted to mean that the hydrocarbon chains are beginning to flex and twist. (This will produce some rotational isomerism, each isomer having its own frequency in this region, producing a smearing-out of the spectrum.) This interpretation is supported by the fact that the band at 719 cm.$^{-1}$ also decreases slightly in intensity. (This band is associated with the in-phase motion of all the $CH_2$ groups, so that twisting of parts of the chain will reduce the intensity of this band.) On further heating to about 120—130° this band decreases considerably in intensity, indicating that

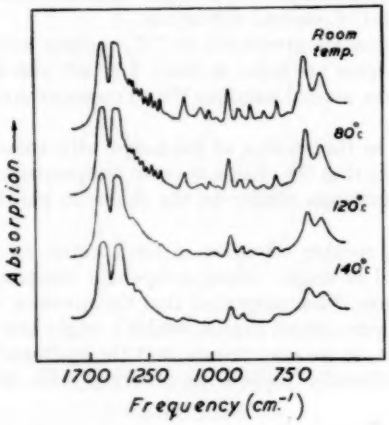



FIG. 3. *Infrared spectra of anhydrous sodium palmitate at different temperatures.*

many more methylene groups are spinning freely about the C–C bonds. All the fine structure in the 1250 cm.$^{-1}$ region vanishes, whilst bands assigned to other $CH_2$ rocking modes also become diffuse or disappear. Bands assigned to methyl rocking modes decrease in intensity but remain prominent. There is little if any movement in frequency of the carboxylate bands at 1560, 1415, or 695 cm.$^{-1}$ but the intensity of the 695 cm.$^{-1}$ band decreases.

Above 120—130° the spectrum of the soap is in fact entirely " liquid-like " in character. The changes observed in the spectra are analogous to those observed in the spectra of, *e.g.*, long-chain monocarboxylic acids when the transition from the crystalline to liquid state occurs. Yet this transition occurs some 160° below the " true " m. p. of the soap. It seems clear that at this temperature the methylene groups are spinning freely and the hydrocarbon chains are in a " liquid state." (The large number of rotational isomers produced causes a smearing out of all the fine structure.) We can conclude that the soap is only prevented from completely melting by the strong bond between the highly polar sodium metal and carboxylate groups. The spectra clearly demonstrate the appearance of the " liquid-crystalline " phase of soaps. *X*-Ray data on this phase support this interpretation, since the long spacings are sharp whilst the short spacings are diffuse.

Little change is observed on further heating of the soap up to 200°, except that the bands at 719 and 695 cm.$^{-1}$ decrease further in intensity and the relative intensity of the 1460 and 1415 cm.$^{-1}$ bands alters. The 1415 cm.$^{-1}$ band then becomes of greater intensity.

On cooling of the soap all these spectral changes are observed in reverse order and all the fine detail in the spectra return.

Analogous spectral changes on heating sodium stearate are observed. These changes can obviously be correlated with the variation of other properties of the soaps at these temperatures, such as flow, yield, and mobility.[18] The increased cohesion and plasticity and fibre-forming properties observed above 110° are doubtless due to the fluidity of the hydrocarbon chains at this temperature.

I thank the Directors of Unilever Limited for permission to publish this paper.

UNILEVER LIMITED, PORT SUNLIGHT, CHESHIRE. [*Received, August 12th*, 1957.]

---

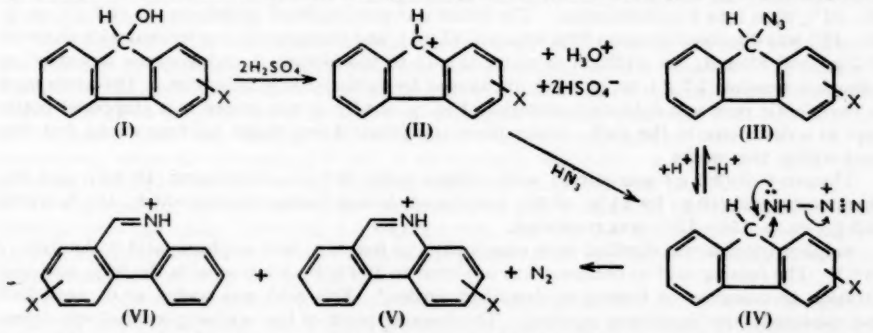
## 153. *Reactions of Organic Azides. Part VIII.*[1] *Kinetics of the Rearrangement of 9-Azidofluorene in Sulphuric–Acetic Acid.*

By C. L. ARCUS and J. V. EVANS.

Rearrangement, in sulphuric–acetic acid, of 9-azidofluorene to phenanthridine is substantially of the first order in the azide with $\log_{10}$ rate linear with $-H_0$ for the medium, at slope slightly greater than unity and an activation energy of ~23·4 kcal./mole. It is concluded that reaction proceeds *via* the monoprotonated azide (which probably exists largely as the ion-pair with bisulphate ion), and that nitrogen-release and the act of rearrangement are simultaneous.

THE conversion, by reaction with hydrazoic and sulphuric acid, of fluoren-9-ols into phenanthridines has been described and discussed in Parts I,[2] III,[3] IV,[4] and VII,[1] attention having been directed to separation and characterisation of mixtures of isomeric phenanthridines, the mechanism of the reaction, and the influence of substituents.

The following observations show that reaction proceeds through formation of the azide (as its proton-adduct): (*a*) from the products of the reaction with fluoren-9-ol [2] and 9-*tert.*-butylfluoren-9-ol,[4] the 9-azidofluorene was isolated; (*b*) on reaction with sulphuric acid, 9-azido-,[2] 9-azido-9-phenyl-,[1] and 9-azido-2-methoxy-fluorene [3] yielded respectively phenanthridine and 9-phenyl- and 2- and 7-methoxy-phenanthridine, the products which are obtained from reaction of the corresponding fluoren-9-ols with hydrazoic and sulphuric




acid. In the reaction of a fluorenol with these acids, the function of the sulphuric acid is two-fold: (i) to convert the alcohol (I) into a carbon cation (II) which, on combination with hydrazoic acid, yields the proton-adduct (IV) of the azide (III); (ii) to maintain a

[1] Part VII, Arcus, Marks, and (in part) Coombs, *J.*, 1957, 4064.
[2] Arcus and Mesley, *J.*, 1953, 178.
[3] Arcus and Coombs, *J.*, 1954, 4319.
[4] Arcus and Lucken, *J.*, 1955, 1634.

substantial proportion of the azide in the protonated state, it being the proton-adduct, not the free azide, which undergoes rearrangement to the phenanthridinium ion (V, VI). That this is so, is shown by observations on secondary azidofluorenes. Thus, although 9-azidofluorene in sulphuric acid liberates nitrogen with rearrangement to the phenanthridinium ion, on long storage or on being heated alone it loses nitrogen to yield 9-iminofluorene.[2] Analogous observations relate to 9-azido-2-nitrofluorene:[3] this compound was never isolated, but 2-nitrofluoren-9-ol gave 2- and 7-nitrophenanthridine on reaction with hydrazoic and sulphuric acid, whereas heating 9-chloro-2-nitrofluorene with sodium azide yielded 9-imino-2-nitrofluorene, presumably by uncatalysed decomposition of the azide. Finally, 9-azido-1 : 2-benzofluorene, heated with trifluoroacetic acid, yields 1 : 2- and 7 : 8-benzophenanthridine, whilst, heated alone, it forms 1 : 2-benzofluorenone imine.[1]

The complexity of the conversion of fluorenol into phenanthridine, and the dual rôle of the strong acid, might be expected to render interpretation of kinetic results for the overall reaction somewhat difficult. It has however been concluded [4] (at least for the two instances in which the azidofluorene accumulated in the reaction mixture to such an extent that it was isolated) that the last stage, (IV) ⟶ (V, VI), is rate-controlling. It was therefore decided to further the investigation of the rearrangement by determining the rate of conversion of 9-azidofluorene into phenanthridine in anhydrous sulphuric–acetic acid solutions. Values of the Hammett acidity function, $H_0$, for sulphuric–acetic acid mixtures, of concentrations suitable for the rearrangement, have been determined by Hall and Spengeman.[5]

## Experimental

M. p.s are corrected.

*9-Azidofluorene.*—To a hot solution of aluminium *iso*propoxide (from aluminium foil, 50 g.; mercuric chloride, 1 g.; propan-2-ol, 800 ml.) was added fluorenone (61 g.) in benzene (250 ml.); the whole was boiled under reflux for 4 hr., the lowest-boiling (acetone) fraction being allowed to distil. Excess of solvent was then distilled under reduced pressure and the viscous residue was poured with stirring into ice-cold 3N-sulphuric acid (3 l.). The precipitate was collected, washed with this acid, then with water, and dried. It (50·5 g.; m. p. 142—143°) was heated with benzene (500 ml.) containing charcoal (1 g.); from the filtered solution there separated fluoren-9-ol (43·5 g.) having m. p. 153—155° and, after further recrystallisation, m. p. 156°. This material was converted by Arcus and Mesley's methods [2] into 9-chlorofluorene (m. p. 90—91°), then into 9-azidofluorene. The latter was recrystallised as follows: it (4·7 g.; m. p. 40—42°) was dissolved in warm 96% ethanol (45 ml.), and the solution was treated with charcoal (0·5 g.) and filtered; on addition of water (4 ml.) to the filtrate, 9-azidofluorene separated as colourless needles (2·7 g.), m. p. 44·5° unchanged by further recrystallisation. The azide used in the kinetic runs was colourless material of m. p. ≮44°; it was stored in a stoppered bottle kept in a desiccator in the dark; under these conditions it was stable for four weeks, but was used within two weeks.

Fluoren-9-ol (3·6 g.) was stirred with sodium azide (2·6 g.), chloroform (40 ml.), and trichloroacetic acid (40 g.) for 2½ hr. at 30°, and the whole was poured into ice-water; the fluorenol (3·5 g.), m. p. 156—157°, was recovered.

Sulphur trioxide was distilled from oleum (26% of free $SO_3$) into sulphuric acid (" AnalaR "; 98%). The fuming acid so obtained was adjusted to 100% by dilution with the 98% acid and titration to cessation of fuming as described earlier.[6] This acid was cooled at 0° until half had solidified; the liquid was rejected. The freezing point of the acid so prepared was determined in a simplified form of Gillespie, Hughes, and Ingold's apparatus; [7] additions of fuming or 98% acid were made where required, in order to attain the maximum freezing point of 10·36—10·39° (uncorr.); little adjustment was necessary.

Acetic acid was twice crystallised by partial solidification, distilled, then thrice recrystallised,

[5] Hall and Spengeman, *J. Amer. Chem. Soc.*, 1940, **62**, 2489.
[6] Arcus, Coombs, and Evans, *J.*, 1956, 1498.
[7] Gillespie, Hughes, and Ingold, *J.*, 1950, 2475.

attaining constant f. p. (determined as above) 16·45°. Sulphuric and acetic acid were kept in capped stoppered bottles.

One ml. of acetic acid dissolved 0·3 g. of 9-azidofluorene, and 0·4 g. of phenanthridine, at 25°.

*Rate Measurements.*—The all-glass reaction vessel comprised a lower, conical, flat-bottomed bulb (*A*) and an upper spherical bulb (*B*); the contents of *B* could be run into *A* through a tap of 4 mm. bore; a pressure-equalising tube connected the tops of *A* and *B*; *A* was fitted with a stoppered (B14) side-arm, and a similar joint connected the top of *B* to the nitrometer. Bulb *B* was placed to one side of the axis of *A*, whereby a shorter form of apparatus was attained.

9-Azidofluorene was weighed into *A*. By pipettes, and the use of a "Pumpett," the requisite amount of sulphuric acid was placed in *B*, and the vessel was reweighed; 50 ml. of acetic acid were then placed in *B* and 10 ml. in *A*, and the whole was again weighed. A Polythene-covered soft-iron stirrer, 3 cm. long, was placed in *A*. The acids in *B* were mixed by rotation of the bulb.

The reaction vessel was then attached to the nitrometer, the tap and joints having been lubricated with a Silicone grease, and immersed in the thermostat. The bulb *A* was placed over a motor-driven rotating magnet; the latter was contained in a water-tight brass box completely immersed in the thermostat bath and fitted with vertical brass tubes acting as vents and carrying the electrical leads. The nitrometer, from which air had been displaced by dry nitrogen, contained transformer oil, and was surrounded by a jacket through which water from the thermostat was circulated by a pump at 300 ml./min. The whole was kept for 1 hr. with the stirrer operating, whereby constant temperature and initial nitrometer reading were attained. The tap connecting *B* with *A* was then opened fully, and the stopwatch started. The time of discharge through the tap was 7—15 sec. depending on the viscosity of the sulphuric–acetic acid solution. Nitrometer readings, at atmospheric pressure, were taken at one-minute intervals for the first 5 min., thereafter less frequently, and finally at 24 hr. In many runs observations were made for a further period. The volume of nitrogen obtained when no further evolution was observed averaged 97·6% of the theoretical. Exceptions were runs at the two lowest acidities at 25°, the latter parts of which were sluggish.

As the run proceeded, the solution became orange and towards the end turbid. It was filtered through a No. 1 sintered-glass filter, and the vessel and precipitate were washed with acetic acid. The precipitate, after being washed with water and methanol, formed a buff powder, m. p. >300°. In ten experiments it averaged 5·2% of the weight of azide used.

The acidic filtrate and washings were diluted with water to 200 ml., neutralised, with cooling and stirring, by ammonia (*d* 0·88, 1 part; water 2 parts), further ammonia (50 ml.) then being added. The precipitated phenanthridine was collected on a No. 1 sintered-glass filter, washed with dilute aqueous ammonia, and dried. It had m. p. 101—103°, and, after recrystallisation from light petroleum (b. p. 60—80°), m. p. 109°. In seven experiments the yield of phenanthridine averaged 94·2%.

By the procedure of mixing the sulphuric acid with the bulk of the acetic acid, and allowing the solution to attain thermostat-temperature before adding it to a solution of the azide in a small portion of the acetic acid, most of the heat of dilution was dissipated before the reaction began. Both in the presence of azide (0·6 g.) and in its absence, where the final concentration of sulphuric acid was 36·5%, the maximum rise in temperature above that of the thermostat, when the contents of *B* and *A* were mixed, was 0·85°; it fell to 0·1° in 30 min.; with acid finally containing 28·5% sulphuric acid, the maximum rise was 0·5°.

In experiments preliminary to the main series it was found that phenanthridine, added initially with the azide, decreased the reaction rate, but did not appreciably lower the final volume of nitrogen evolved. At the ends of the present runs, the excess of sulphuric acid over phenanthridine was from 20- to 106-fold.

It was noticed in experiments without azide that, during the first 2 min. after the contents of *B* had run into *A*, there was a small evolution of gas. This is ascribed to displacement of gas dissolved in the acetic acid in *A* on addition of the sulphuric–acetic acid. For acids finally containing 25·5 and 36·5% sulphuric acid, at 25°, the volume evolved in each case averaged 1·2 ml.; by extrapolation of the readings for the first few minutes of azide runs back to zero time, it was found that an identical initial evolution had occurred, *i.e.*, that the latter is a physical displacement unaffected by the presence of azide. The initial evolution was markedly less when higher reaction-temperatures were used. For the slower azide runs, correction for the initial evolution was made by extrapolation as above, and for the fastest runs by addition

XUM

to the pre-mixing nitrometer-reading of the volume found to be evolved in a parallel non-azide run.

Vapour pressures of sulphuric–acetic acid mixtures have not been recorded; corrections (about 0·01 atm. at 25°) were made on the assumption that acetic acid is dimeric, and that sulphuric acid forms a 1 : 1-molecular complex with acetic acid. In a solution composed of $p$ moles of sulphuric and $q$ of acetic acid, the molar fraction of dimer is $(q - p)/(q + p)$, and the recorded vapour pressures of acetic acid were reduced by this factor. The volume of evolved nitrogen, reduced to ml. at N.T.P., $x$, was plotted against time, $t$ (min.); $t_{0\cdot5}$ and $t_{0\cdot7}$, the times for evolution of half and seven-tenths of the volume ($a$) equimolar with the weight of azide taken, were ascertained. $\Delta x/\Delta t$ was plotted against $t$, and $\log_{10}(\mathrm{d}x/\mathrm{d}t)$ then plotted against $\log_{10}(a - x)$. Such plots were substantially linear, and the initial intercept gave $\log_{10}(\mathrm{d}x/\mathrm{d}t)_{t=0}$, from which was derived the initial pseudo-first-order constant $k_i$, in min.$^{-1}$. The slope of the logarithmic plot was in general greater than unity, the average dependence on $(a - x)$ being to power 1·20. Of the minor factors modifying the individual run, detailed above, initial temperature rise and the formation of phenanthridine tend to raise the apparent order; the influence on order of the formation of a small amount of non-phenanthridine by-product is not readily deducible. The determination of $k_i$, $t_{0\cdot5}$, $t_{0\cdot7}$, yielding comparable values at three points in the course of each run, is considered to be the most satisfactory treatment of the experimental data.

## Results and Discussion

Fluorenone was satisfactorily reduced to fluoren-9-ol by aluminium *iso*propoxide; reduction with this reagent is preferable to that, used hitherto, with sodium amalgam. Unlike 9-phenyl- and 1 : 2-benzo-fluoren-9-ol, the unsubstituted compound did not yield the azidofluorene on treatment with trichloroacetic acid and sodium azide; it was recovered.

A series of runs with different initial concentrations of 9-azidofluorene was carried out at 25°, in acetic acid containing 34·1% sulphuric acid, whence $H_0$ is −4·01. The plot of $\log_{10}(\mathrm{d}x/\mathrm{d}t)_{t=0}$ *versus* $\log_{10} a$ (Fig. 1) is substantially linear at slope 1·09. $\mathrm{Log}_{10} t_{0\cdot5}$ and $\log_{10} t_{0\cdot7}$, when similarly plotted, have slope −0·04 and −0·02; it can be shown [8] that

$$\log t_{\text{fraction}} = \text{Constant} - (n - 1)\log a$$

where $t_{\text{fraction}}$ is the time required for a given fraction of the total reaction to occur, and $n$ the reaction-order, whence, in the present instance, the times for half and seven-tenths completion yield reaction-order 1·04 and 1·02 respectively. From the three sets of data it is concluded that the reaction is essentially first-order in 9-azidofluorene; this accords with the mechanism, involving the rate-controlling decomposition of the protonated azide, which has been deduced for the rearrangement on non-kinetic grounds.

Runs were next made with sulphuric–acetic acid solutions containing from 10·1 to 36·5% sulphuric acid, and hence having $H_0$ from −2·87 to −4·85. The results are given in Fig. 2, where $\log_{10} k_i$, $-\log_{10} t_{0\cdot5}$, and $-\log_{10} t_{0\cdot7}$ are plotted against $-H_0$. (The values of $-\log_{10} t_{0\cdot5}$ are equal to the logarithms of the pseudo-first-order reaction constants measured over the times for half reaction, together with a numerical constant, and similarly for $-\log_{10} t_{0\cdot7}$.) The slopes of the straight lines drawn through these sets of points are, respectively, 1·03, 1·07, and 1·09.

It is not believed that linearity between log rate and $-H_0$ extends to acidities much below those of Fig. 2. Preliminary experiments, during which practicable conditions for kinetic measurements were being sought, implied that there exists a threshold of acidity below which decomposition does not occur. These experiments also showed reaction, at the same concentration of sulphuric acid, to be markedly faster in nitromethane than in acetic acid.

The data of Fig. 2 imply that the rate-determining step of the reaction proceeds either through the monoprotonated azide (IV; X = H) formed in fractionally small amount

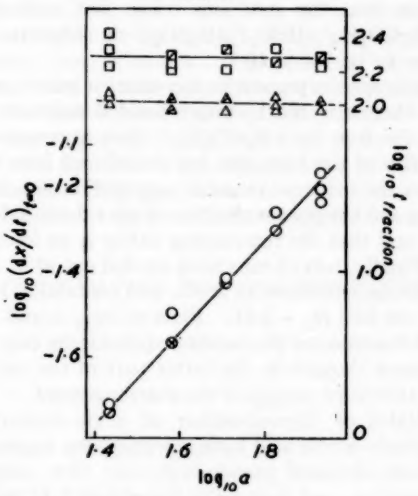
[8] Frost and Pearson, "Kinetics and Mechanism," Wiley, New York, 1953, pp. 40—42.

from the azide (III), or through the diprotonated azide (VIII or IX), formed in fractionally small amount from the otherwise completely monoprotonated azide.

$$R{\cdot}NH{\cdot}\overset{+}{N}{:}N \overset{H^+}{\rightleftharpoons} R{\cdot}\overset{+}{N}H_2{\cdot}\overset{+}{N}{:}N \text{ (VIII) or } R{\cdot}NH{\cdot}\overset{+}{N}{:}\overset{+}{N}H \text{ (IX)}$$

While the second alternative is not excluded, it appears the less probable because rearrangement through (IX) implies the separation of protonated nitrogen, whereas

FIG. 1.




FIGS. 1, 2, and 3.

*Rearrangement of 9-azidofluorene in sulphuric–acetic acid.*

○ $\log_{10}(dx/dt)_{t=0}$ or $\log_{10} 10^4 k_1$.

△ $\log_{10} f_{0.5}$.

□ $\log_{10} f_{0.7}$.

Two coincident points are marked /, and three ×.

FIG. 2.

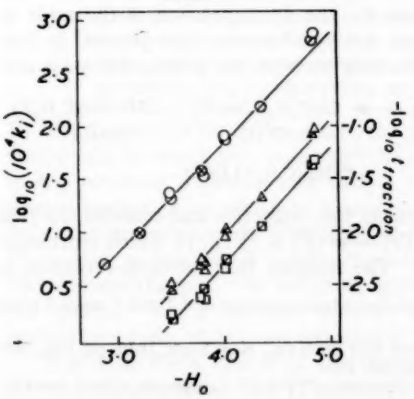
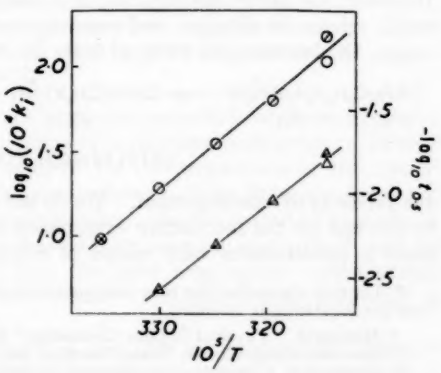



FIG. 3.




nitrogen has no manifest basic properties, and rearrangement through (VIII) implies either the formation of doubly protonated phenanthridine, or, since accommodation of a second proton is hardly possible, the ejection of a proton at the act of rearrangement.

Description of some aspects of the mechanism of the acid catalysis requires a brief account of conditions in the sulphuric–acetic acid solution. Acetic acid is considered to

exist in the liquid state as the dimer.[10,11,12] From the following results it is concluded that sulphuric acid forms a complex with acetic acid: (*a*) the plot of viscosity *versus* composition has a marked maximum at the equimolar point;[13] (*b*) the freezing points of mixtures of the acids may indicate a 1 : 1 compound;[14] (*c*) the heat of dilution of sulphuric by acetic acid is qualitatively large; no measurement appears to have been recorded. The conductometric and potentiometric investigations of Kolthoff and his co-workers,[15] and Smith and Elliott,[16] lead to the conclusion that the sulphuric–acetic acid complex is mainly a hydrogen-bonded entity, in equilibrium with a relatively small proportion of the ion pair $CH_3{\cdot}CO_2H_2^+HSO_4^-$, which in turn is dissociated only to a small extent into the free ions. The last authors find the classical dissociation constant ($[CH_3{\cdot}CO_2H_2^+][HSO_4^-]/[H_2SO_4]$) of sulphuric acid in acetic acid containing 0·12% of water to be $7{\cdot}4 \times 10^{-9}$.

The species present in the solution which are capable of donating a proton to the azide are, therefore, the hydrogen-bonded sulphuric–acetic acid complex, the ion-pair, above, and the free ion $CH_3{\cdot}CO_2H_2^+$, their aggregate protonating effect being measured by the activity of the hydrogen ion as deduced from the indicator studies on which $H_0$ is based. From the evidence on ionic aggregation in acetic acid, it is probable that the protonated azide and the phenanthridinium ion exist in solution largely as the ion-pairs with bisulphate ion, and that the rearranging entity is an ion-pair rather than a free cation.

Finally, sets of runs were carried out at 5° intervals from 25° to 45°, at constant initial azide concentration, in acetic acid containing 17·2% of sulphuric acid, whence the medium had (at 25°) $H_0$ −3·21. Plots of $\log_{10} k_i$ and $-\log_{10} t_{0\cdot5}$ against $1/T$ (Fig. 3; $t_{0\cdot7}$ was not used because, at the acidity applying in this series, at the lower temperatures, reaction becomes sluggish in the latter part of the run) yield values 24·0 and 22·8 kcal./mole for the activation energy of the rearrangement.

Rates of decomposition of azido-diphenylmethanes and -1 : 1-diphenylethanes in sulphuric–acetic acid have recently been reported by Gudmundsen and McEwen.[17] These authors obtained pseudo-first-order rate constants for approximately the first 50% of completion, and found the logarithms * to be linear, at unit slope, with values of $-H_0$ for the medium; for azidodiphenylmethane, the energy of activation was found to be 21·2 kcal./mole. These experimental findings are similar to those of the present work. However, the above authors deduce a mechanism for the decomposition of the azide in which release of nitrogen and rearrangement are not synchronous, but proceed in two stages, the intermediate (XI), of finite life, intervening between the protonated azide and

$$\underset{\text{(X)}}{CRPh(C_6H_4X){\cdot}NH{\cdot}\overset{+}{N}{:}N} \longrightarrow \underset{\text{(XI)}}{CRPh(C_6H_4X){\cdot}\overset{+}{N}H} + N_2 \longrightarrow \underset{\text{(XII)}}{CR(C_6H_4X){:}\overset{+}{N}HPh} + \underset{\text{(XIII)}}{CRPh{:}\overset{+}{N}H(C_6H_4X)}$$

$$\text{(XIV) } CPh(C_6H_4X){:}NH \qquad COPh(C_6H_4X) \text{ (XV)}$$

the products of rearrangement. We do not concur in this deduction and consider reaction to proceed by the mechanism exemplified in [(IV) ⟶ (V) + (VI)], in which rearrangement is simultaneous with release of nitrogen. The findings that nitrogen-evolution is

* The text states that the rate constants were plotted, but a later equation and Table 1 make it clear that the logarithm is intended.

[9] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, 1940, pp. 265, 267.
[10] Mackenzie and Winter, *Trans. Faraday Soc.*, 1948, **44**, 159.
[11] Partington, "An Advanced Treatise on Physical Chemistry," Vol. II, Longmans, Green and Co., London, 1951, pp. 160—161.
[12] Landee and Johns, *J. Amer. Chem. Soc.*, 1941, **63**, 2891.
[13] Drucker and Kassel, *Z. physikal. Chem.*, 1911, **76**, 367; Hall and Voge, *J. Amer. Chem. Soc.*, 1933, **55**, 243.
[14] Kendall, *ibid.*, 1921, **43**, 1832; Lehrman, *Trans. Amer. Inst. Chem. Eng.*, 1926, **18**, 187.
[15] Kolthoff and Willman, *J. Amer. Chem. Soc.*, 1934, **56**, 1007; Kolthoff and Bruckenstein, *ibid.*, 1956, **78**, 1.
[16] Smith and Elliott, *ibid.*, 1953, **75**, 3566.
[17] Gudmundsen and McEwen, *ibid.*, 1957, **79**, 329.

of the first order in azide and that the plot of log rate *versus* $-H_0$ has unit slope do not permit distinction between these two mechanisms, since both postulate a unimolecular decomposition of the monoprotonated azide.

However, with regard to the products from Gudmundsen and McEwen's mechanism, it appears probable that the intermediate (XII; R = H), formed from an azidodiphenylmethane, would release a proton to yield the imine (XIV), and, on hydrolysis, the benzophenone (XV). These products are those corresponding to hydrogen-migration, and such products are stated [17] never to have been isolated in any of the azido-reactions of diarylmethanols. In the acid-catalysed decomposition of azidofluorenes, the 9-iminofluorenes and fluorenones, the analogues of (XIV) and (XV), have not been encountered. In contrast, as stated earlier, the imine is the characteristic product of the non-catalysed (*e.g.*, pyrolytic) decomposition of a secondary 9-azidofluorene. Further, with regard to the acid-catalysed reaction, it has been found [4] that a 9-*tert.*-butyl group, which can neither conjugate not hyperconjugate, slows down the rearrangement of the azide, compared with reaction in the presence of groups which can conjugate (ethyl, *iso*propyl, phenyl); this accords with the formation of an aromatic ring simultaneously with nitrogen release but not with the formation of the fluorenyl analogue of (XI), in which such aromatisation does not occur. It is concluded that (XI) is not formed, and that migration synchronises with release of nitrogen.

We thank the Government Grants Committee of the Royal Society and Imperial Chemical Industries Limited for grants.

BATTERSEA COLLEGE OF TECHNOLOGY, LONDON, S.W.11. [*Received, September 25th*, 1957.]

---

## 154. *The Structure of Ruscogenin.*

By D. BURN, B. ELLIS, and V. PETROW.

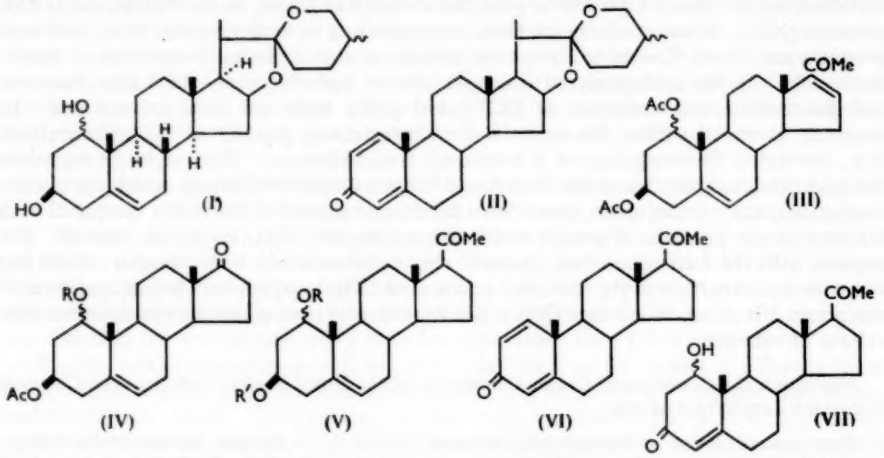
*Ruscus aculeatus* L., derived from Belgian sources, yields a *ca.* 1 : 1 mixture of ruscogenin (25D) and *neo*ruscogenin (25L). Degradation of this mixture gives an excellent yield of 1ξ : 3β-diacetoxypregna-5 : 16-dien-20-one (III), the structure of which follows from its transformations. The constitutions 25D- and 25L-spirost-5-ene-1ξ : 3β-diol (I) are consequently assigned to ruscogenin and *neo*ruscogenin, respectively.

IN 1955 Lapin and Sannié [1] reported the presence in *Ruscus aculeatus* L. of a new sapogenin, ruscogenin, to which they assigned [2] the constitution of a 19-hydroxydiosgenin. In view of the potential importance of such a raw material for the preparation of the 19-norsteroid hormones, we obtained a supply of *Ruscus aculeatus* L. from Belgian sources and isolated therefrom a genin with physical constants similar to those reported for ruscogenin. In contrast to the French results, degradation showed that our genin was a 1ξ- (I) and not 19-hydroxydiosgenin. In addition, infrared data furnished presumptive evidence that our product was a mixture of 25D- and 25L-forms. Our conclusions, published in preliminary form,[3,4] are now reported in full.

Whilst in Paris, one of us was told by Dr. H. Lapin that his independent findings [5] now led him to favour the 1ξ-hydroxy-structure (I). Our "ruscogenin," as anticipated in the preliminary communication, is a *ca.* 1 : 1-mixture of the 25D- (ruscogenin) and what

[1] Lapin and Sannié, *Bull. Soc. chim. France*, 1955, 1552.
[2] Sannié and Lapin, *ibid.*, p. 1556.
[3] Burn, Ellis, and Petrow, *Proc. Chem. Soc.*, 1957, 119.
[4] Petrow, Burn, and Ellis, XVIth Internat. Congr. Pure Appl. Chem., Résumés des Communications, Vol. II, p. 264.
[5] Lapin and Delépine, *Compt. rend.*, 1957, **244**, 3065.

appears to be the newly isolated [6] 25L-form (*neo*ruscogenin). This follows from (i) the identity of the infrared spectra of our "ruscogenin" with those of the authentic 25D- and 25L-forms (kindly supplied by Dr. H. Lapin) in all regions, except for the intensities of the bands near 920 and 900 cm.$^{-1}$ which are diagnostic of configuration at $C_{(25)}$, (ii) the preparation, after extensive fractionation, of pure ruscogenin diacetate from our genin




mixture (see p. 797), and (iii) the isolation, in considerably greater than 50% yield, of a single pregnane derivative by standard side-chain degradation of our sample. Slight differences in experimental findings between the two groups arose from the different proportions of the two forms present in our crude genin and in that available to Dr. H. Lapin, which had been derived from French sources and was markedly richer in the 25D-isomer. Our degradative studies had moreover been performed on the *ca.* 1 : 1 mixture of the 25D- and 25L-forms, as we had been interested primarily in pregnane and androstane derivatives obtainable from either.

Oppenauer oxidation of our ruscogenin (25D + 25L) gave, in low yield, a ketone to which the constitution 25L-spirosta-1 : 4-dien-3-one (II) is assigned, the 1 : 4-dien-3-one system being established by its ultraviolet spectrum [7] ($\lambda_{max.}$ 244·5 mμ) and that of the derived 2 : 4-dinitrophenylhydrazone [8] ($\lambda_{max.}$ 402 mμ). The 25L-configuration follows from comparison of the infrared spectrum with that of authentic 25D-spirosta-1 : 4-dien-3-one (II) (with which it is not chemically identical, see p. 797), revealing virtually identical bands except in the region 920—900 cm.$^{-1}$ (see above).[9] In addition, the 25D- and 25L-dienones have nearly identical optical rotations, in accord with the generalisation [10] that epimerisation at $C_{(25)}$ has a negligible effect on optical rotation. Fractionation of the mother-liquors from the Oppenauer oxidation did not yield the expected 25D-dienone, probably owing to the unsatisfactory nature of the oxidation which gave only the 25L-isomer in very low yield after exhaustive purification.

Degradation of the sapogenin side-chain of "ruscogenin" by standard procedures furnished 1ξ : 3β-diacetoxypregna-5 : 16-dien-20-one (III), which was further degraded by Beckmann rearrangement of its oxime and subsequent mild reacetylation to 3β-acetoxy-1ξ-hydroxyandrost-5-en-17-one (IV; R = H); more vigorous acetylation gave the diacetate (IV; R = Ac).

[6] Sannié and Lapin, XVIth Internat. Congr. Pure Appl. Chem., Résumés des Communications, Vol. II, p. 261.
[7] Cf. Dorfman, *Chem. Rev.*, 1953, **53**, 68.
[8] Djerassi and Ryan, *J. Amer. Chem. Soc.*, 1949, **71**, 1000.
[9] Wall, Eddy, McClennan, and Klumpp, *Analyt. Chem.*, 1952, **24**, 1337.
[10] Wall, *Experientia*, 1955, **11**, 340.

XUM

Partial hydrogenation of the diene (III) gave 1ξ : 3β-diacetoxypregn-5-en-20-one (V; R = R′ = Ac), which differed from the 3β : 19-diacetoxypregn-5-en-20-one previously obtained from strophanthidin.[11] The diacetate (V; R = R′ = Ac) with methanolic potassium hydroxide afforded the diol (V; R = R′ = H) which passed into 1-dehydroprogesterone [12,13] (VI) on Oppenauer oxidation, albeit in low yield. The same end-product was obtained by microbiological oxidation of the diol (V; R = R′ = H) with *Corynebacterium mediolanum* to 1ξ-hydroxyprogesterone (VII), followed by dehydration with methanolic alkali.

The two hydroxyl groups in the diol (V; R = R′ = H) differ in reactivity. Treatment of the diacetate (V; R = R′ = Ac) with aqueous methanolic potassium hydrogen carbonate leads to a monoacetate, regarded as 1ξ-acetoxy-3β-hydroxypregn-5-en-20-one (V; R = Ac; R′ = H) as it readily gives a sparingly soluble digitonin complex. Mild acetylation of the diol (V; R = R′ = H) furnished the isomeric 3β-acetoxy-1ξ-hydroxypregn-5-en-20-one (V; R = H; R′ = Ac) which failed to react with digitonin. These observations are analogous to those reported for 1α : 3β-diols of the cholestane [14] and 5α-etiocholanic acid [15] series. However, in the absence of experimental results relating to the behaviour of isomeric 1β : 3β-diols, our findings do not justify an assignment of configuration to the 1-hydroxyl group of (V; R = R′ = H) and of ruscogenin (I). The 1β-configuration is attractive on biogenetic grounds.

## Experimental

Optical rotations refer to $CHCl_3$ solutions. Ultraviolet (in EtOH) and infrared (in $CS_2$) absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc., of this laboratory and by Dr. A. E. Kellie of the Courtauld Institute of Biochemistry. Alumina of B.D.H. chromatography grade was used.

*Genin Mixture.*—As isolated from *R. aculeatus* and crystallised from aqueous methanol, the genin mixture (*ca.* 1 : 1 25D and 25L) formed plates, m. p. 197—199°, $[\alpha]_D^{21}$ −106° (*c* 0·58), $\nu_{max.}$ 898, 922 cm.$^{-1}$ (approximately equal intensity) (Found: C, 71·7; H, 9·5. Calc. for $C_{27}H_{42}O_4,H_2O$: C, 72·3; H, 9·9%). Lapin and Sannié [1] give m. p. 197—202°, $[\alpha]_D^{16}$ −119°, and, after extensive drying, m. p. 205—210°, $[\alpha]_D^{19}$ −127°.

*Ruscogenin Diacetate.*—The genin mixture (1·8 g.) in acetic anhydride (120 ml.) containing toluene-*p*-sulphonic acid (0·05 g.) was kept at room temperature for 2 hr. The product was isolated with ether and repeatedly crystallised from methanol. Ruscogenin diacetate formed needles, m. p. 190—192°, $[\alpha]_D^{20}$ −68° (*c* 0·33), $\nu_{max.}$ 899 > 921 cm.$^{-1}$ (Found: C, 71·7; H, 9·2. Calc. for $C_{31}H_{46}O_6$: C, 72·3; H, 9·0%). Lapin and Sannié [1] give m. p. 192—194°. The constants of *neo*ruscogenin diacetate (kindly supplied by Dr. H. Lapin), as determined by us, were m. p. 132—134°, $[\alpha]_D$ −64°, $\nu_{max.}$ 921 > 900 cm.$^{-1}$.

Hydrolysis of the 25D-diacetate afforded ruscogenin hydrate, m. p. 210—213°, $[\alpha]_D^{25}$ −116° (*c* 0·76) (Found: C, 72·9; H, 10·0%).

25L-*Spirosta*-1 : 4-*dien*-3-*one*.—A solution of the genin mixture (0·3 g.) in toluene (18 ml.) and *cyclo*hexanone (3 ml.) was distilled to remove water, aluminium *iso*propoxide in toluene (25% w/v; 1 ml.) was added, and the mixture was refluxed for 4 hr. The product was chromatographed in benzene on silica (20 g.). Elution with benzene–ether (9 : 1) gave a gum which crystallised from aqueous methanol, to give 25L-*spirosta*-1 : 4-*dien*-3-*one* as needles, m. p. 206—209°, $[\alpha]_D^{23}$ −77·2° (*c* 0·32), $\lambda_{max.}$ 245 mμ (ε 15,174), $\nu_{max.}$ 1658, 1624, 1605 cm.$^{-1}$ (1 : 4-dien-3-one) (in $CHCl_3$), 922 > 897 cm.$^{-1}$ (Found: C, 78·4; H, 8·5. $C_{27}H_{38}O_2$ requires C, 79·0; H, 9·3%); the mixed m. p. with the 25D-isomer (see below) was 177—186°. The 2 : 4-*dinitrophenylhydrazone* (prepared in ethanol–phosphoric acid) formed dark red needles, m. p. 243—244° (decomp.), $\lambda_{max.}$ 402 mμ (ε 34,200) (Found: C, 67·1; H, 6·85; N, 9·25. $C_{33}H_{42}O_6N_4$ requires C, 67·1; H, 7·2; N, 9·5%), after crystallisation from acetone–ethanol.

[11] Ehrenstein and Dünnenberger, *J. Org. Chem.*, 1956, **21**, 774.
[12] Vischer, Meystre, and Wettstein, *Helv. Chim. Acta*, 1955, **38**, 835.
[13] Sondheimer, Velasco, and Rosenkranz, *J. Amer. Chem. Soc.*, 1955, **77**, 5673.
[14] Striebel and Tamm, *Helv. Chim. Acta*, 1954, **37**, 1094.
[15] Sallmann and Tamm, *ibid.*, 1956, **39**, 1340.

25D-*Spirosta*-1 : 4-*dien*-3-*one*.—To 5α : 25D-spirostan-3-one (tigogenone) (3·65 g.) in acetic acid (150 ml.), bromine (4·1 g., 3 equiv.) in acetic acid (25 ml.) was added dropwise with stirring. The resulting purple solution was kept at room temperature overnight and then poured into water. The precipitated solids crystallised from dichloromethane–methanol, to yield moderately pure 2α : 4α : 23ξ-tribromo-5α : 25D-spirostan-3-one as needles, m. p. 192° (decomp.). No attempt was made to separate the $C_{(23)}$ isomers. The total product (1·55 g.) was heated with collidine (15 ml.) under reflux for 2 hr. The precipitated hydrobromide (0·93 g.) was removed and the product was isolated with ether. Purification from methanol yielded 23ξ-bromo-25D-spirosta-1 : 4-dien-3-one as needles, m. p. 192—195°. The last compound (1·8 g.) was heated under nitrogen with acetic acid (60 ml.) containing sodium iodide [16] (6 g.) on the steam-bath for 30 hr. and the product was isolated with ether–benzene. Purification from aqueous acetone gave 25D-spirosta-1 : 4-dien-3-one as needles, m. p. 198—200°, $[\alpha]_D^{24}$ −70·4° (*c* 0·64), $\lambda_{max.}$ 244·5 mμ (ε 15,280), $\nu_{max.}$ 1659, 1621, 1604 cm.$^{-1}$ (1 : 4-dien-3-one) (in $CHCl_3$), 921 < 898 cm.$^{-1}$ (Found: C, 78·4; H, 9·25%). Miki and Hara [17] give m. p. 186° and no other constants.

*Degradation of the Genin Mixture*.—The genin (15 g.) was heated under reflux for 2·5 hr. with acetic anhydride (30 ml.) and pyridine (15 ml.) containing methylamine hydrochloride (5 g.). The mixture was poured into water and extracted with ether. The ethereal extract was washed with dilute acid, aqueous sodium carbonate, and water, dried ($Na_2SO_4$), and evaporated under reduced pressure. The residual gum was purified from methanol, to yield *ψ-ruscogenin triacetate* as laths, m. p. 96—98°, $[\alpha]_D^{22}$ ±0° (*c* 1·0) (Found: C, 70·9; H, 8·7. $C_{33}H_{48}O_7$ requires C, 71·2; H, 8·7%).

A solution of this triacetate (10 g.) in acetic acid (100 ml.) was treated slowly, with stirring, with chromium trioxide (2·9 g.) in acetic acid (30 ml.). After 1 hr. the mixture was poured into water, and the product was isolated with ether and boiled with acetic acid (50 ml.) under reflux for 2 hr. The residue obtained on evaporation under reduced pressure was dissolved in ether, the ethereal solution was washed with aqueous sodium carbonate and water, dried ($Na_2SO_4$), and evaporated. Chromatography of the residue in benzene solution on alumina (150 g.) gave 1ξ : 3β-*diacetoxypregna*-5 : 16-*dien*-20-*one* (III) as needles, m. p. 127—129°, $[\alpha]_D^{23}$ ±0° (*c* 0·8), $\lambda_{max.}$ 239·5 mμ (ε 9,250) (Found: C, 72·8; H, 8·5. $C_{25}H_{34}O_5$ requires C, 72·4; H, 8·3%), after purification from acetone–hexane.

The foregoing compound (5 g.) in ethanol (100 ml.) was treated at room temperature with hydroxylamine hydrochloride (5 g.) and sodium acetate (7·5 g.) in water (20 ml.) for 48 hr. Dilution with water precipitated the crystalline *oxime*, stout needles, m. p. 188—192°, $[\alpha]_D^{25}$ +5·1° (*c* 0·78), $\lambda_{max.}$ 236 mμ (ε 14,930) (Found: C, 69·6; H, 8·0; N, 3·3. $C_{25}H_{35}O_5N$ requires C, 69·9; H, 8·2; N, 3·25%), after crystallisation from aqueous methanol.

3β-*Acetoxy*-1ξ-*hydroxyandrost*-5-*en*-17-*one* (IV; R = H).—A solution of the foregoing oxime (4·75 g.) in dry pyridine (50 ml.) containing toluene-*p*-sulphonyl chloride (5 g.) was kept at 0° for 18 hr. The solution was then poured slowly into ice-cold 10% sulphuric acid (300 ml.), and the resulting suspension was kept at room temperature for a further 3 days. The product was isolated with ether as a gum which was reacetylated with acetic anhydride–pyridine on the steam-bath for 1 hr. The product precipitated with water was chromatographed in benzene on alumina (40 g.); elution with the same solvent gave a gum which, purified from acetone–hexane, gave 3β-*acetoxy*-1ξ-*hydroxyandrost*-5-*en*-17-*one*, needles, m. p. 94—98°, $[\alpha]_D^{21}$ +17·85° (*c* 0·62), $\lambda_{max.}$ 294 mμ (ε 34) (Found: C, 72·3; H, 9·15. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%).

1ξ : 3β-*Diacetoxyandrost*-5-*en*-17-*one* (IV; R = Ac).—The foregoing monoacetate (0·35 g.) was treated with acetic anhydride (5 ml.) containing toluene-*p*-sulphonic acid (0·05 g.) at room temperature for 2 hr. Dilution with water and recrystallisation of the product from acetone–hexane gave 1ξ : 3β-*diacetoxyandrost*-5-*en*-17-*one* as needles, m. p. 149—151°, $[\alpha]_D^{20}$ +20·7° (*c* 0·99), $\lambda_{max.}$ 294 mμ (ε 41) (Found: C, 71·6; H, 8·6. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%).

1ξ : 3β-*Diacetoxypregn*-5-*en*-20-*one* (V; R = R′ = Ac).—The corresponding diene (III) (2 g.) was hydrogenated in ethanol (100 ml.) in the presence of 2% palladium–barium carbonate (0·4 g.) at room temperature and pressure. After removal of the catalyst, dilution with water gave a solid which was recrystallised from aqueous methanol, to yield 1ξ : 3β-diacetoxypregn-5-en-20-one as needles, m. p. 166—168°, $[\alpha]_D^{22}$ +45·4° (*c* 0·74), $\lambda_{max.}$ 286 mμ (ε 45) (Found: C, 71·8; H, 8·7. Calc. for $C_{25}H_{36}O_5$: C, 72·1; H, 8·7%). Lapin and Delépine [5] give m. p. 160—162° $[\alpha]_D$ +54°.

[16] Kirk, Patel, and Petrow, *J.*, 1957, 1046.
[17] Miki and Hara, *Pharm. Bull.* (*Japan*), 1956, **4**, 421.

1ξ : 3β-*Dihydroxypregn-5-en-20-one* (V; R = R′ = H).—The diacetate (V; R = R′ = Ac) (1·7 g.) in methanol (50 ml.) was treated with potassium hydroxide (4·6 g.) in water (15 ml.) for 18 hr. at room temperature. Dilution with water gave solids which, purified from aqueous methanol, yielded 1ξ : 3β-dihydroxypregn-5-en-20-one as laths, m. p. 187—190°, $[\alpha]_D^{19}$ +26·2° (*c* 0·81) (Found: C, 75·4; H, 9·3. Calc. for $C_{21}H_{32}O_2$: C, 75·8; H, 9·7%). Lapin and Delépine [8] give m. p. 186—188°, $[\alpha]_D$ +34°.

1-*Dehydroprogesterone* (VII). —A solution of the foregoing diol (1·15 g.) in toluene (40 ml.) and *cyclo*hexanone (10 ml.) was distilled to remove 10 ml. A solution of aluminium *iso*propoxide in toluene (25% w/v; 4 ml.) was added and the mixture heated under reflux for 0·5 hr. The product crystallised from aqueous methanol, unchanged diol (0·3 g.; m. p. and mixed m. p. 188—190°) separating. Chromatography of the solids left in the mother-liquors in benzene on alumina (30 g.) afforded 1-dehydroprogesterone, prisms, m. p. 155—157°, $[\alpha]_D^{20}$ +131·7° (*c* 0·88), $\lambda_{max.}$ 244 mμ (ε 16,740) (Found: C, 80·9; H, 8·8. Calc. for $C_{21}H_{28}O_2$: C, 80·7; H, 9·0%), after crystallisation from acetone–hexane. The m. p. was not depressed on admixture with an authentic sample kindly provided by Dr. A. Wettstein.

1ξ-*Hydroxyprogesterone* (VIII) (with Mrs. I. A. Stuart-Webb, B.Sc., and Mrs. A. Carmichael, B.Sc.).—The diol (V; R = R′ = H) (0·2 g.) was oxidised microbiologically with *Corynebacterium mediolanum*. The product, isolated with chloroform, crystallised from acetone–hexane to give 1ξ-*hydroxyprogesterone* as needles, m. p. 153°, $[\alpha]_D^{23}$ +192° (*c* 0·11), $\lambda_{max.}$ 240·5 mμ (ε 14,500) (Found: C, 76·3; H, 9·2. $C_{21}H_{30}O_3$ requires C, 76·4; H, 9·1%).

Treatment of this material (8 mg.) with methanolic potassium hydroxide for 1 hr. under reflux yielded 1-dehydroprogesterone, m. p. 138—143°, $\nu_{max.}$ 1660 (1 : 4-dien-3-one), 1707 cm.$^{-1}$ (20-ketone), mixed m. p. with an authentic sample 144—147°.

1ξ-*Acetoxy*-3β-*hydroxypregn-5-en*-20-*one* (V; R = Ac, R′ = H).—To a solution of the diacetate (V; R = R′ = Ac) (2 g.) in methanol (200 ml.) was added potassium hydrogen carbonate (5 g.) in water (100 ml.), and the mixture was kept at room temperature for 18 hr. Dilution with water and extraction with ether afforded a gum which was crystallised from aqueous methanol, to give 1ξ-*acetoxy*-3β-*hydroxypregn-5-en*-20-*one* as needles, m. p. 161—163°, $[\alpha]_D^{21}$ +50° (*c* 0·93) (Found: C, 73·3; H, 9·05. $C_{23}H_{34}O_4$ requires C, 73·7; H, 9·15%).

3β-*Acetoxy*-1ξ-*hydroxypregn-5-en*-20-*one* (V; R = H, R′ = Ac).—A solution of the diol (V; R = R′ = H) (0·7 g.) in acetic acid (3 ml.) and acetic anhydride (1 ml.) was kept for 2 hr. at 60° and a further 2 days at room temperature. The product was isolated with ether and crystallised from acetone–hexane, unchanged diol (0·3 g.; m. p. and mixed m. p. 187—190°) separating. Chromatography of the solids left in the mother-liquors in benzene on alumina (20 g.) afforded 3β-*acetoxy*-1ξ-*hydroxypregn-5-en*-20-*one* as plates, m. p. 188—190°, $[\alpha]_D^{24}$ +31·2° (*c* 0·63) (Found: C, 73·6; H, 9·6. $C_{23}H_{34}O_4$ requires C, 73·7; H, 9·15%), after crystallisation from aqueous methanol.

The authors thank Dr. J. Forrest, Ph.D., for assistance in the isolation of the genins and the Directors of The British Drug Houses Ltd., for permission to publish this work.

Chemical Research Laboratories,
The British Drug Houses Ltd., London, N.1. [*Received, September 16th*, 1957.]

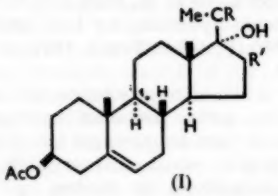
## 155. *Modified Steroid Hormones. Part VIII.* Some* 16-*Bromo- and* 16-*Chloro-derivatives of Testosterone.*

By B. Ellis, D. Patel, and V. Petrow.

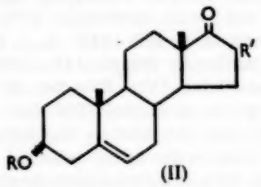
Methods are described for the preparation of 16α- and 16β-bromo- and 16-chloro-androstenediones and their conversion, with the exception of the 16α-bromo-isomer, into the corresponding 16-halogenotestosterones.

The compounds named in the title were required for biological study.

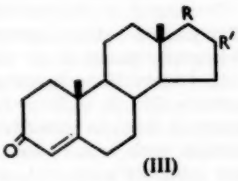
When the oxime (I; R = :N·OH, R′ = Br) derived from 3β-acetoxy-16β-bromo-17α-hydroxypregn-5-en-20-one [1] (I; R = :O, R′ = Br) was treated with phosphorus oxychloride in pyridine, Beckmann rearrangement followed by degradation to 3β-acetoxy-16β-bromoandrost-5-en-17-one (II; R = Ac, R′ = β-Br) occurred [cf. the conversion of 3β-acetoxy-17α-hydroxypregn-5-en-30-one oxime (I; R = :N·OH, R′ = H) into dehydro*epi*androsterone acetate (II; R = Ac, R′ = H) under similar experimental conditions [2]]. Debromination of the 16-bromo-ketone (II; R = Ac, R′ = β-Br) with chromous chloride [3] gave dehydro*epi*androsterone acetate. Hydrolysis with methanolic hydrochloric acid



(I)



(II)



(III)

afforded the corresponding alcohol (II; R = H, R′ = β-Br) which passed into 16β-bromoandrost-4-ene-3 : 17-dione (III; R = :O, R′ = β-Br) on brief Oppenauer oxidation. The last compound was reduced with sodium borohydride under conditions favouring the conversion of both oxo-functions into hydroxyl groups to give material which was oxidised selectively at $C_{(3)}$. The resulting 16 : 17-bromohydrin passed smoothly into androst-4-ene-3 : 17-dione (III; R = :O, R′ = H) when warmed with methanolic alkali, an observation establishing its constitution as 16β-bromo-17β-hydroxyandrost-4-en-3-one (16β-bromotestosterone) (III; R = β-OH, R′ = β-Br).

Treatment of 3β : 17-diacetoxyandrosta-5 : 16-diene [4] with two equivalents of bromine, followed by brief reaction of the product with sodium iodide in acetone, led to a monobromo-ketone, which passed into dehydro*epi*androsterone acetate on reduction with chromous chloride. This compound differed from the 16β-bromo-ketone (II; R = Ac, R′ = β-Br), and is therefore formulated as the isomeric 3β-acetoxy-16α-bromoandrost-5-en-17-one (II; R = Ac, R′ = α-Br). Its hydrolysis with methanolic hydrochloric acid gave 16α-bromo-3β-hydroxyandrost-5-en-17-one (II; R = H, R′ = α-Br) in excellent yield, no evidence for inversion at $C_{(16)}$ being obtained. This is a somewhat surprising result as Fajkoš has shown [5] that in the saturated androstane series the 16α-bromo-17-ketones are thermodynamically less stable than their 16β-isomers into which they are converted by alkaline or acidic reagents. Treatment of the 16α-bromo-17-ketone (II; R = Ac, R′ = α-Br) with hydrogen bromide in acetic acid afforded only an intractable gum (cf. Fajkoš [5]). Brief Oppenauer oxidation of the alcohol (II; R = H, R′ = α-Br

* Part VII, *J.*, 1957, 4112.

[1] Romo and De Vivar, *J. Org. Chem.*, 1956, **21**, 902; Patel, Petrow, and Stuart-Webb, *J.*, 1957 665.

[2] B.P. 747,793; Schmidt-Thomé, *Annalen*, 1957, **603**, 43.

[3] Rosenkranz, Mancera, Gatica, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4077.

[4] Moffet and Weisblat, *ibid.*, 1952, **74**, 2183.

[5] Fajkoš, *Coll. Czech. Chem. Comm.*, 1955, **20**, 312.

gave 16α-bromoandrost-4-ene-3 : 17-dione (III; R = :O, R′ = α-Br), no evidence for the concomitant formation of the 16β-epimer (III; R = :O, R′ = β-Br) being obtained. Attempts to convert the 16α-isomer (III; R = :O, R′ = α-Br) into 16α-bromotestosterone proved disappointing, however, as reduction with sodium borohydride under conditions similar to those employed by Norymberski and Woods [6] for the preparation of testosterone from androst-4-ene-3 : 17-dione, or with excess of sodium borohydride or lithium aluminium hydride followed by selective oxidation at $C_{(3)}$, furnished in each case a complex mixture from which a pure species could not be isolated.

Epoxide ring fission of 3β-acetoxy-16α : 17α-epoxypregn-5-en-20-one with hydrogen chloride gave 3β-acetoxy-16β-chloro-17α-hydroxypregn-5-en-20-one (I; R = :O, R′ = β-Cl), which was converted *via* the oxime into 3β-acetoxy-16β-chloroandrost-5-en-17-one (II; R = Ac, R′ = β-Cl). The last compound proved inert to chromous chloride (cf. the similar stability of 2α-chlorocholestan-3-one [7]), but was readily reduced to dehydro*epi*androsterone acetate by zinc dust in acetic acid. Acid hydrolysis furnished the alcohol (II; R = H, R′ = β-Cl), converted by Oppenauer oxidation into 16β-chloroandrost-4-ene-3 : 17-dione (III; R = :O, R′ = β-Cl). When the latter compound was treated with a limited quantity of sodium borohydride under carefully controlled conditions, selective reduction of the 17-oxo-group occurred with formation of a 16 : 17-chlorohydrin, also obtained by reduction of both oxo-groups present in the ketone (III; R = :O, R′ = β-Cl) followed by preferential oxidation at $C_{(3)}$. The product passed into androst-4-ene-3 : 17-dione on being warmed with alkali, and is hence regarded as 16β-chloro-17β-hydroxyandrost-4-en-3-one (16β-chlorotestosterone) (III; R = β-OH, R′ = β-Cl).

3β-Acetoxy-5 : 6-dibromoandrostan-17-one in carbon tetrachloride was treated with one equivalent of chlorine to give a mixture from which a dibromomonochloro-ketone was isolated in *ca.* 40% yield. Debromination of the last compound with sodium iodide in acetone gave an unsaturated 16-chloro-ketone which differed from the 16β-chloro-derivative (II; R = Ac, R′ = β-Cl) and is therefore regarded as the isomeric 3β-acetoxy-16α-chloroandrost-5-en-17-one (II; R = Ac, R′ = α-Cl). Acid hydrolysis gave the alcohol (II; R = OH, R′ = α-Cl), converted by brief Oppenauer oxidation into 16α-chloroandrost-4-ene-3 : 17-dione (III; R = :O, R′ = α-Cl). Prolonged Oppenauer oxidation, in contrast, was accompanied by epimerisation of the 16-halogen atom with the formation of the thermodynamically more stable 16β-chloroandrost-4-ene-3 : 17-dione (see above). Transformation of the 16α-epimer (III; R = :O, R′ = α-Cl) into the required 16α-chloro-17β-hydroxyandrost-4-en-3-one (16α-chlorotestosterone) (III; R = β-OH, R′ = α-Cl) was effected by reduction with an excess of sodium borohydride and subsequent preferential oxidation of the $C_{(3)}$-allylic alcohol group.

3β-Acetoxy-16α : 17α-epoxypregn-5-en-20-one proved resistant to anhydrous hydrogen fluoride under the conditions employed by Fried and Sabo [8] for the preparation of 9α-fluorohydrocortisone acetate from 21-acetoxy-9α : 11α-epoxy-17α-hydroxypregn-4-ene-3 : 20-dione. A similar failure to effect epoxide ring fission of 11-oxo-16α : 17α-epoxypregnanes with hydrogen fluoride has been reported.[9]

## Experimental

Optical rotations were measured for $CHCl_3$ solutions in a 1 dm. tube. Ultraviolet absorption spectra were kindly determined (for EtOH solutions) by Mr. M. T. Davies, B.Sc.

*3β-Acetoxy-16β-bromo-17α-hydroxypregn-5-en-20-one Oxime.*—Hydroxylamine hydrochloride (2·1 g.) and anhydrous sodium acetate (2·4 g.) in water (10 ml.) were added to 3β-acetoxy-16β-bromo-17α-hydroxypregn-5-en-20-one [1] (4·5 g.) in ethanol (75 ml.) and the mixture kept at

[6] Norymberski and Woods, *J.*, 1955, 3426.
[7] Ellis and Petrow, *J.*, 1953, 3869.
[8] Fried and Sabo, *J. Amer. Chem. Soc.*, 1957, **79**, 1130.
[9] Beyler and Hoffmann, *J. Org. Chem.*, 1956, **21**, 572.

room temperature for 2 days. Careful addition of water gave crystals (2·8 g.) which were purified from aqueous methanol. The *oxime* separated in flat needles, m. p. 175° (decomp.), $[\alpha]_D^{23}$ −3° (*c* 0·76) (Found: C, 59·2; H, 7·4. $C_{23}H_{34}O_4NBr$ requires C, 59·0; H, 7·3%). The compound was not obtained by employing brief reaction periods at the b. p.

3β-*Acetoxy*-16β-*bromoandrost*-5*e*-*n*-17-*one*.—The foregoing oxime (5·8 g.) in pyridine (30 ml.) was treated at 0° with phosphorus oxychloride (5 g.) in pyridine. After 2 hr. at 0°, the mixture was poured into water and the solids were crystallised from aqueous methanol. The *bromoketone* (4·2 g.) formed needles, m. p. 175—176°, $[\alpha]_D^{20}$ +39° (*c* 1·1) (Found: C, 61·8; H, 7·2. $C_{21}H_{29}O_3Br$ requires C, 61·6; H, 7·1%).

It (0·5 g.) in acetone (30 ml.) under carbon dioxide was treated for 15 min. with chromous chloride solution [3] (10 ml.). The product was purified from aqueous methanol, to give dehydro*epi*androsterone acetate, m. p. and mixed m. p. 169—170°.

16β-*Bromo*-3β-*hydroxyandrost*-5-*en*-17-*one*.—The foregoing bromo-ketone (5 g.) in methanol (100 ml.) and concentrated hydrochloric acid (5 ml.) was heated under reflux for 1 hr. Addition of water gave the *alcohol* (4·1 g.), blades (from aqueous methanol), m. p. 176—177°, $[\alpha]_D^{20}$ +61° (*c* 0·92) (Found: C, 62·2; H, 7·6. $C_{19}H_{27}O_2Br$ requires C, 62·1; H, 7·4%).

16β-*Bromoandrost*-4-*ene*-3 : 17-*dione*.—A solution of the foregoing alcohol (4 g.) in toluene (180 ml.) and *cyclo*hexanone (40 ml.) was distilled until 40 ml. of distillate had collected. After the addition of aluminium *iso*propoxide (2·5 g.) in toluene (10 ml.), the mixture was refluxed for 10 min., cooled, and washed with dilute sulphuric acid. Organic solvents were removed by steam-distillation and the product was extracted into methylene dichloride. Addition of ether to the dried and concentrated extract gave a solid (2·6 g.; m. p. 174—175°) which was purified from acetone–hexane. 16β-*Bromoandrost*-4-*ene*-3 : 17-*dione* formed prisms, m. p. 182°, $[\alpha]_D^{23}$ +184° (*c* 0·98), $\lambda_{max.}$ 239·5 mμ (log ε 4·23) (Found: C, 62·6; H, 6·5. $C_{19}H_{25}O_2Br$ requires C, 62·5; H, 6·9%).

16β-*Bromotestosterone*.—The foregoing compound (1 g.) in methanol (200 ml.) was treated with sodium borohydride (250 mg.) and set aside overnight. After addition of a few drops of acetic acid, most of the solvent was removed *in vacuo* and the product isolated with ether. Crystallisation from acetone–hexane gave material (0·9 g.), m. p. 142—143°, which was oxidised (Oppenauer) at room temperature to 16β-*bromotestosterone* (0·41 g.), prisms (from methanol), m. p. 191—193°, $[\alpha]_D^{25}$ +73° (*c* 1·03), $\lambda_{max.}$ 240 mμ (log ε 4·22) (Found: C, 62·0; H, 7·1. $C_{19}H_{27}O_2Br$ requires C, 62·1; H, 7·4%).

Brief warming with 5% methanolic potassium hydroxide gave androst-4-ene-3 : 17-dione, identified by direct comparison with an authentic specimen.

3β-*Acetoxy*-16α-*bromoandrost*-5-*en*-17-*one*.—Bromine (11·5 g.) in methylene dichloride (100 ml.) was added dropwise during 30 min. to a stirred solution of 3β : 17-diacetoxyandrosta-5 : 16-diene [4] (13·1 g.) in methylene dichloride (200 ml.) at 0°. After being washed successively with aqueous sodium thiosulphate, aqueous sodium hydrogen carbonate, and water, the mixture was dried and the solvent removed *in vacuo*. A suspension of the solid residue in acetone (200 ml.) was treated with sodium iodide (25 g.), and the mixture stirred for 5 min., and then poured into an excess of aqueous sodium thiosulphate. The precipitate was washed, air-dried, and crystallised from acetone–methanol. 3β-*Acetoxy*-16α-*bromoandrost*-5-*en*-17-*one* (10·9 g.) formed plates or needles, m. p. 186°, $[\alpha]_D^{20}$ −27° (*c* 1·02) (Found: C, 61·5; H, 7·4. $C_{21}H_{29}O_3Br$ requires C, 61·6; H, 7·1%).

Treatment with chromous chloride gave dehydro*epi*androsterone acetate, identified by m. p. and mixed m. p.

16α-*Bromo*-3β-*hydroxyandrost*-5-*en*-17-*one*.—The foregoing bromo-ketone (10·5 g.) in chloroform (50 ml.) was treated with methanol (500 ml.) and concentrated hydrochloric acid (10 ml.). The mixture was agitated for 2 days, the solvents were removed *in vacuo*, and the residue was purified from aqueous methanol. 16α-*Bromo*-3β-*hydroxyandrost*-5-*en*-17-*one* separated in fluffy needles (8·4 g.), m. p. 179—180°, $[\alpha]_D^{20}$ −20° (*c* 0·79) (Found: C, 61·7; H, 7·5. $C_{19}H_{27}OBr$ requires C, 62·1; H, 7·4%).

16α-*Bromoandrost*-4-*ene*-3 : 17-*dione*.—A solution of the foregoing alcohol (8·4 g.) in toluene (360 ml.) and *cyclo*hexanone (80 ml.) was distilled until 80 ml. of distillate had collected. After the addition of aluminium *iso*propoxide (5 g.) in toluene (20 ml.), the mixture was refluxed for 10 min., cooled rapidly, and washed with dilute sulphuric acid and then with water. Solvents were removed by steam-distillation and the product was extracted into methylene dichloride. Addition of ether to the dried and concentrated extract gave a solid (5·9 g.; m. p. 161—162°).

XUM

**16α-*Bromoandrost-4-ene*-3 : 17-*dione*** crystallised from acetone–hexane in prisms, m. p. 165—166°, $[\alpha]_D^{20}$ +112° (*c* 0·97), $\lambda_{max.}$ 239·5 mμ (log ε 4·21) (Found: C, 62·6; H, 7·1. $C_{19}H_{25}O_2Br$ requires C, 62·5; H, 6·9%).

**3β-*Acetoxy*-16β-*chloro*-17α-*hydroxypregn*-5-*en*-20-*one***.—Concentrated hydrochloric acid (10 ml.) was added to 3β-acetoxy-16α : 17α-epoxypregn-5-en-20-one (10 g.) in acetic acid (120 ml.). After 1 hr. at room temperature, the mixture was poured into water and the precipitated solid crystallised from aqueous ethanol, to give the ***chlorohydrin*** (9·1 g.), plates, m. p. 167—168°, $[\alpha]_D^{22}$ −36° (*c* 1·04) (Found: C, 68·0; H, 8·0. $C_{23}H_{33}O_4Cl$ requires C, 67·5; H, 8·1%).

The ***oxime***, prepared by heating the chlorohydrin (3·7 g.) in ethanol (50 ml.) under reflux for 30 min. with hydroxylamine hydrochloride (2·1 g.) and anhydrous sodium acetate (2·4 g.) in water (5 ml.), crystallised from aqueous ethanol in needles, m. p. 207—208° (decomp.), $[\alpha]_D^{22}$ −17° (*c* 0·98) (Found: C, 65·0; H, 8·1. $C_{23}H_{34}O_4NCl$ requires C, 65·2; H, 8·1%).

**3β-*Acetoxy*-16β-*chloroandrost*-5-*en*-17-*one***.—Phosphorus oxychloride (5 ml.) in pyridine (15 ml.) was added dropwise during 10 min. to the foregoing oxime (7 g.) in pyridine (30 ml.). After 2 hr. at 0°, the mixture was poured into water and the solids were purified from aqueous methanol. **3β-*Acetoxy*-16β-*chloroandrost*-5-*en*-17-*one*** (5 g.) formed needles, m. p. 174—175°, $[\alpha]_D^{20}$ +25° (*c* 0·67) (Found: C, 69·5; H, 7·9; Cl, 9·6. $C_{21}H_{29}O_3Cl$ requires C, 69·1; H, 8·0; Cl, 9·7%). The compound was recovered unchanged after treatment with the chromous chloride reagent. The compound (200 mg.) was heated for 10 min. at 100° with zinc dust (2 g.) and acetic acid (7 ml.). The product (120 mg.) was crystallised from aqueous methanol and identified as dehydro*epi*androsterone acetate.

**16β-*Chloro*-3β-*hydroxyandrost*-5-*en*-17-*one***.—The foregoing chloro-ketone (5 g.) in methanol (100 ml.) and concentrated hydrochloric acid (5 ml.) was heated under reflux for 1 hr. Purification of the product from aqueous methanol gave the ***alcohol*** (4 g.), needles or plates, m. p. 158—160°, $[\alpha]_D^{25}$ + 38° (*c* 0·74) (Found: C, 70·0; H, 8·3. $C_{19}H_{27}O_2Cl$ requires C, 70·7; H, 8·4%).

**16β-*Chloroandrost*-4-*ene*-3 : 17-*dione***.—The foregoing alcohol (4 g.) was oxidised under the same conditions as those employed for the preparation of 16β-bromoandrost-4-ene-3 : 17-dione (above). The product was crystallised from acetone–hexane, to give **16β-*chloroandrost*-4-*ene*-3 : 17-*dione*** (2·4 g.), prisms, m. p. 173—174°, $[\alpha]_D^{20}$ +190° (*c* 1·02), $\lambda_{max.}$ 239·5 mμ (log ε 4·22) (Found: C, 70·7; H, 7·8; Cl, 11·2. $C_{19}H_{25}O_2Cl$ requires C, 71·1; H, 7·8; Cl, 11·1%).

**16β-*Chlorotestosterone***.—(*a*) Sodium borohydride (100 mg.) was added to a solution of the foregoing compound (436 mg.) in methanol (100 ml.) at 5°. After 45 min. at this temperature, the mixture was treated with a few drops of acetic acid, most of the solvent was removed *in vacuo*, and the product was isolated with ether. Crystallisation from acetone–hexane gave **16β-*chlorotestosterone*** (295 mg.), needles, m. p. 194—196°, $[\alpha]_D^{22}$ +89° (*c* 1·01), $\lambda_{max.}$ 240 mμ (log ε 4·20) (Found: C, 70·6; H, 8·6; Cl, 10·9. $C_{19}H_{27}O_2Cl$ requires C, 70·7; H, 8·4; Cl, 11·0%).

(*b*) 16β-Chloroandrost-4-ene-3 : 17-dione (1·3 g.) in methanol (300 ml.) was treated with sodium borohydride (500 mg.) for 18 hr. at room temperature. The product was isolated with ether and oxidised at room temperature (Oppenauer). Crystallisation gave 16β-chlorotestosterone (0·98 g.), identical with a specimen prepared by method (*a*) above.

The **17β-*propionate*** separated from acetone–hexane in needles, m. p. 126—128°, $[\alpha]_D^{22}$ +136° (*c* 1·02) (Found: C, 69·9; H, 8·2; Cl, 9·7. $C_{22}H_{31}O_3Cl$ requires C, 69·7; H, 8·2; Cl, 9·4%).

When the foregoing compound (300 mg.) in methanolic potassium hydroxide (5 ml. of 4%) was heated under reflux for 10 min., and water added to turbidity, there was obtained androst-4-ene-3 : 17-dione (150 mg.), m. p. 170—172°, not depressed in admixture with an authentic specimen.

**3β-*Acetoxy*-5 : 6-*dibromo*-16α-*chloroandrostan*-17-*one***.—3β-Acetoxy-5 : 6-dibromoandrostan-17-one [10] (49 g.) in carbon tetrachloride (1170 ml.) was treated at room temperature with chlorine (6·8 g.) in acetic acid (100 ml.). Absorption of chlorine was complete after 3 days. The mixture was washed with aqueous sodium hydrogen carbonate, then with water, and kept for several hours at 0°. The crystalline precipitate (22 g., m. p. 164—165°) was collected and purified from acetone, to give **3β-*acetoxy*-5 : 6-*dibromo*-16α-*chloroandrostan*-17-*one***, needles, m. p. 168—170° (decomp.), $[\alpha]_D^{20}$ −11° (*c* 0·96) (Found: C, 48·3; H, 5·5. $C_{21}H_{29}O_3Br_2Cl$ requires C, 48·1; H, 5·5%).

Examination of the carbon tetrachloride mother-liquor led to the isolation of a dichloro-derivative (6 g.), dense prisms (from methylene dichloride–methanol), m. p. 175—176° (decomp.), $[\alpha]_D^{20}$ −4°, which consistently failed to give satisfactory analytical data.

[10] Levy and Jacobsen, *J. Biol. Chem.*, 1947, **171**, 71.

**3β-*Acetoxy*-16α-*chloroandrost*-5-*en*-17-*one*.**—Sodium iodide (30 g.) was added to the foregoing 16α-chloro-5 : 6-dibromide (15·7 g.) in acetone (250 ml.). The mixture was stirred for 30 min., then poured into an excess of aqueous sodium thiosulphate, and the precipitated solids (9·3 g., m. p. 178—180°) were crystallised from methylene dichloride–methanol. **3β-*Acetoxy*-16α-*chloroandrost*-5-*en*-17-*one*** formed dense prisms, m. p. 188—190°, $[\alpha]_D^{25}$ −5° (*c* 0·71) (Found: C, 69·2; H, 8·0; Cl, 9·6. $C_{21}H_{29}O_3Cl$ requires C, 69·1; H, 8·3; Cl, 9·8%). The compound was unaffected by the chromous chloride reagent. Reduction with zinc and acetic acid gave dehydro*epi*androsterone acetate.

**16α-*Chloro*-3β-*hydroxyandrost*-5-*en*-17-*one*.**—Methanol (1200 ml.) and concentrated hydrochloric acid (15 ml.) were added to the foregoing compound (15 g.) in methylene dichloride (40 ml.), and the mixture set aside for 2 days. Solvents were removed *in vacuo* and the residue was purified from aqueous methanol, to give the ***alcohol*** (11·5 g.), needles, m. p. 179—180°, $[\alpha]_D^{25}$ +1° (*c* 0·98) (Found: C, 68·3; H, 8·7; Cl, 9·7. $C_{19}H_{27}O_3Cl,CH_3{\cdot}OH$ requires C, 67·7; H, 8·7; Cl, 10·0%).

**16α-*Chloroandrost*-4-*ene*-3 : 17-*dione*.**—The foregoing alcohol (11·5 g.) was oxidised for 10 min. under conditions similar to those employed for the preparation of 16α-bromoandrost-4-ene-3 : 17-dione (above). Crystallisation of the product from acetone–hexane gave **16α-*chloroandrost*-4-*ene*-3 : 17-*dione*** (6·1 g.), m. p. 179—180°, $[\alpha]_D^{23}$ +159° (*c* 0·57), $\lambda_{max.}$ 239·5 mμ (log ε 4·19) (Found: C, 70·7; H, 8·0. $C_{19}H_{25}O_2Cl$ requires C, 71·1; H, 7·8%). In admixture with 16β-chloroandrost-4-ene-3 : 17-dione a m. p. depression of 25° was obtained.

When the reaction time was extended to 3 hr. the product was only 16β-chloroandrost-4-ene-3 : 17-dione (30%), m. p. and mixed m. p. 171—173°.

**16α-*Chlorotestosterone*.**—16α-Chloroandrost-4-ene-3 : 17-dione (6 g.) in methanol (1 l.) was treated with sodium borohydride (2·5 g.) and set aside overnight. After addition of acetic acid (3 ml.), most of the solvent was removed *in vacuo*, and the product isolated with ether. Treatment with acetone (50 ml.) gave an insoluble fraction (1·4 g.; m. p. 202—204°; no ultraviolet absorption; positive Rosenheim reaction) which was discarded. The acetone-soluble fraction was oxidised at room temperature (Oppenauer). **16α-*Chlorotestosterone*** (2·7 g.) separated from acetone–hexane in prisms, m. p. 198—199°, $[\alpha]_D^{23}$ +60° (*c* 0·92), $\lambda_{max.}$ 240 mμ (log ε 4·20) (Found: C, 70·4; H, 8·8. $C_{19}H_{27}O_2Cl$ requires C, 70·7; H, 8·4%).

The compound was recovered mostly unchanged after being heated under reflux for 30 min. with 2·5% methanolic potassium hydroxide.

The **17β-*propionate*** crystallised from aqueous ethanol in needles, m. p. 223—225°, $[\alpha]_D^{23}$ +27° (*c* 1·01) (Found: C, 69·5; H, 8·1. $C_{22}H_{31}O_3Cl$ requires C, 69·7; H, 8·2%).

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this work.

CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES LTD., LONDON, N.1. [*Received, October 11th*, 1957.]

---

## 156. *Potential Anti-purines. Part I. The Synthesis of Derivatives of 8-Thiapurine (2-Thia-1 : 3 : 4 : 6-tetra-azaindene) by a New Reaction.*

By G. M. TIMMIS.

A new reaction is described for the synthesis of derivatives of 8-thiapurine (2-thia-1 : 3 : 4 : 6-tetra-azaindene) from 4-amino-5-nitrosopyrimidines and thiourea, and its mechanism is discussed.

OF recent years the conception has been developed that, by the use in chemotherapy of substances with anti-purine activity, an interference with nucleic acid biosynthesis might be caused which might be usefully reflected in the inhibition of the growth of viruses and possibly even in some partially selective inhibition of malignant growth. This conception is supported by the incorporation of 2-amino-6-hydroxy-8-azapurine [1] (8-azaguanine) and 6-mercaptopurine [2] into the nucleic acids of mice and rats and of 8-azaguanine into tobacco

[1] Mitchell, Skipper, and Bennett, *Cancer Res.*, 1950, **10**, 647.
[2] Elson, Bieber, and Hitchings, *Ann. New York Acad. Sci.*, 1954, **60**, 297.

mosaic virus causing loss of infectivity.[3] 6-Mercaptopurine is useful in the treatment of leukæmias.[4] A new reaction has now yielded derivatives of 8-thiapurine (2-thia-1 : 3 : 4 : 6-tetra-azaindene) (I) which are potential anti-purines because of a degree of structural similarity to purine.

Thiourea and the appropriate 4-amino-5-nitrosopyrimidine (II; shown in the tautomeric form) were fused together and yielded, with evolution of steam, the corresponding "thiapurine" (I), usually in yields of over 50%. The temperature required for the reaction varies from 145° to 185° according to the solubility and reactivity of the nitrosopyrimidine. The best solvent for the reaction is, in general, molten thiourea used in the necessary excess. Thiourea and 4-amino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-5-nitroso-2 : 4-dioxopyrimidine, dispersed in tetrahydronaphthalene, reacted satisfactorily, however, with the evolution of only a trace of ammonia and no hydrogen sulphide. The reaction has been applied to the synthesis of 8-thiatheophylline and 6-hydroxy-3-methyl-2-oxo-2 : 3-dihydro- and 2 : 6-diamino-8-thiapurine (I; $R = R' = NH_2$).

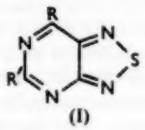
The diaminothiapurine, on hydrolysis with aqueous hydrochloric acid, yielded 2-amino-6-hydroxy-8-thiapurine (I; $R = OH$, $R' = NH_2$) which was purified by sublimation under reduced pressure. The structure was confirmed by synthesis from 2 : 4 : 5-triamino-6-hydroxypyrimidine and thionyl chloride. The structures of the three thiapurines made by the new method were similarly confirmed. The conditions used by Blicke and Godt [5] for the known method were modified by the use of thionyl chloride without any solvent and by using the conveniently prepared bisulphite salt of the 4 : 5-diaminopyrimidine in some cases instead of the base. The structures were similarly confirmed of 6-amino- and 2 : 6-dihydroxy-8-thiapurine, previously obtained in only poor yield by the action of sulphur dichloride on 4 : 5 : 6-triaminopyrimidine, and of sulphuryl chloride on 4 : 5 : 6-triamino-2-methylthiopyrimidine respectively.[6]

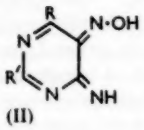
The advantage of the new method over the old is that one stage, reduction of the 4-amino-5-nitrosopyrimidine to the diamine, is avoided with a consequent saving of time and improvement in yield.

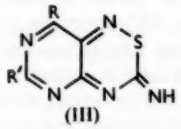
Since the new reaction must involve an intermediate stage, the three alternative possibilities for its structure have been tested in preliminary experiments and two of them eliminated, thus pointing to the probable mechanism of the reaction. Thus the dihydro-imino-2-thiatetra-azanaphthalene (III) might have been formed by condensation of *iso*thiocyanic acid (from the thiourea) with the imino-group of the imino-oxime (II) and subsequent cyclodehydrogenation effected in some way by the oxygen of the oxime group with consequent loss of water. Similarly the isomer (IV) could conceivably arise by initial condensation of *iso*thiocyanic acid with the oxime group. Conversion of these structures into an 8-thiapurine would require loss of hydrocyanic acid, but this could not be detected in the gaseous products of the reaction either by the delicate benzidine cupric acetate colour reaction or by examination of the infrared spectrum. The remaining possibility involves the reaction of *iso*thiourea and the imino-oxime (II), probably by condensation between the mercapto- and the oxime groups to form the compound (VII), with loss of water. Analogous known reactions which support this suggested condensation are the formation of 5-anilino-3-phenyl-1 : 2 : 4-thiadiazole [7] (VI) from the condensate [8] (V) of benzamidoxime and phenyl *iso*thiocyanate, the conversion (by a Beckmann rearrangement) of *O*-acetylbenzaldoxime into thiobenzamide by the action of sodium hydrogen sulphide [9] and formation of 5 : 6-dihydro-7 : 8 : 8-trimethyl-4 : 7-methanobenz*iso*thiadiazole from

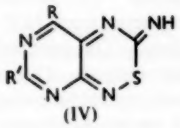
[3] Matthews, *J. Gen. Microbiol.*, 1954, **10**, 521.
[4] Burchenal, Ellison, Murphy, Karnofsky, Sykes, Tan, Mermann, Yuceoglu, Myers, Krakoff, and Alberstadt, *Ann. New York Acad. Sci.*, 1954, **60**, 359.
[5] Blicke and Godt, *J. Amer. Chem. Soc.*, 1954, **76**, 2798.
[6] Schrage and Hitchings, *J. Org. Chem.*, 1951, **16**, 207.
[7] Koch, *Ber.*, 1891, **24**, 394.
[8] Kruger, *Ber.*, 1884, **17**, 1060.
[9] Anger and Billy, *Compt. rend.*, **136**, 556.

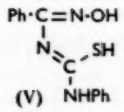
hydrogen sulphide and β-camphorquinone dioxime.[10] The fact that a substantial amount of water is liberated in the reaction, coupled with a yield of the thiapurine of over 50%, argues against its formation from (VII) by hydrolysis of the formamidino-group as urea and subsequent cyclodehydrogenation of the resulting oxime. The remaining alternative to be considered is therefore fission of formamidine from (VII) and simultaneous ring closure. Since formamidine itself was unlikely to be isolable from the reaction mixture,

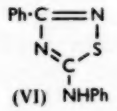

(I)

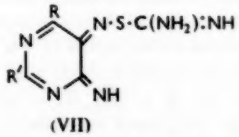

(II)


(III)


(IV)


(V)


(VI)


(VII)

further evidence was sought by treating 5-ethyl-5-1′-methylbutyl(thiobarbituric) acid with 4-amino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-5-nitroso-2 : 6-dioxopyrimidine since the cyclised formamidine structure (pyrimidine) presumably formed would be more stable than formamidine and therefore isolable; but only a small yield of 8-thiatheophylline could be isolated after reaction at the abnormally high temperature required for this condensation.

## Experimental

Analyses are by Mr. P. R. W. Baker and by the Microanalytical Laboratory, Imperial College of Science and Technology, London.

*Synthesis of 8-Thiapurines (2-Thia-1 : 3 : 4 : 6-tetra-azaindenes) from 4-Amino-5-nitroso-pyrimidines and Thiourea.*—Thiourea (1·8 g.) and 4-amino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-5-nitroso-2 : 4-dioxopyrimidine (0·9 g.) were finely powdered, mixed, and heated in an oil-bath until a bath temperature of about 160° was reached; the mixture melted, the red colour of the pyrimidine disappeared, and brisk effervescence occurred; the temperature was held constant for 2—3 min., *i.e.*, until the reaction was finished. The light yellow melt was cooled and triturated with cold water (7 ml.), to remove unchanged thiourea, and the solid collected, dried, and sublimed at 140°/1 mm. The white microcrystalline sublimate of 8-thiatheophylline (0·7 g., 72%), m. p. 185°, gave, on recrystallisation from water, needles (0·53 g., 55%), m. p. 186° (Found: C, 36·6; H, 2·9; N, 28·3; S, 15·9. Calc. for $C_6H_6O_2N_4S$: C, 36·4; H, 3·0; N, 28·3; S, 16·1%). This compound was also obtained as needles, m. p. 154° (cf. Blicke and Godt [7]), and the two forms were interconvertible sometimes merely on storage. Water vapour evolved during the reaction condensed in the upper part of the tube. The condensate was shown to be water (containing ammonia), by boiling it off on heating the tube at 104°, by contact with anhydrous copper sulphate which became blue and by determination of the refractive index.

Thiourea (3 g.) and 2 : 4 : 6-triamino-5-nitrosopyrimidine (1·5 g.) were mixed and heated in a bath at 170—175°. The reaction was completed in 4 min., the melt triturated with water, the solid collected, extracted with 0·5N-sodium hydroxide, washed, and extracted again with boiling 20% aqueous acetic acid, and the extract was basified with ammonia solution, yielding a brick-red crystalline precipitate (0·8 g.), m. p. 353°. Sublimation at 230°/1 mm. yielded yellow microcrystalline 2 : 6-*diamino-8-thiapurine* (0·7 g.), which crystallised from water as yellow needles, m. p. 355° (Found: C, 28·3; H, 2·6; N, 49·8; S, 18·8. $C_4H_4N_6S$ requires C, 28·6; H, 2·4; N, 50·0; S, 19·0%). Identity with the product synthesised from tetra-aminopyrimidine and thionyl chloride was indicated by a mixed m. p.

Thiourea (1 g.) and 4-amino-2 : 3-dihydro-6-hydroxy-3-methyl-5-nitroso-2-oxopyrimidine (0·5 g.) were heated together at 185—190° until the reaction was finished (3 min.). After

[10] Sen, *J. Indian Chem. Soc.*, 1938, **15**, 537.

trituration with water (5 ml.) the solid was collected, dried, and sublimed at 150°/1 mm., yielding white needles (0·24 g.), m. p. 217°. Recrystallisation from water yielded 2 : 3-*dihydro*-6-*hydroxy*-3-*methyl*-2-*oxo*-8-*thiapurine* as either long slender or very short prisms, m. p. 219° (Found: C, 32·6; H, 2·1; N, 30·7; S, 17·0. $C_5H_4O_2N_4S$ requires C, 32·6; H, 2·2; N, 30·4; S, 17·4%), identified by mixed m. p. with the product from thionyl chloride and the diaminopyrimidine (see below).

Thiourea (0·42 g., 1·1 mol.) and 4-amino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-5-nitroso-2 : 4-dioxopyrimidine (0·9 g.) were dispersed in tetrahydronaphthalene (10 ml.), all materials being anhydrous, and heated in an oil-bath at 160—165° for 15 min.; water and a trace of ammonia were evolved but no hydrogen sulphide. After cooling, the liquid was separated and mixed with light petroleum (b. p. 40—60°; 30 ml.); crude 8-thiatheophylline (0·35 g.) separated. Also, the sticky solid deposited from the mixture was washed with ether and triturated with water, to yield crude thiapurine. On sublimation the crude material yielded pure 8-thiatheophylline (0·4 g.), m. p. 154°, identified by mixed m. p. and analysis (Found: C, 36·5; H, 3·2; N, 28·0%).

Under fusion conditions the reaction appears to be catalysed by the admixture of 10% of anhydrous sodium acetate with the nitroso-compound, since the required temperature is then lowered by about 10°.

*Reaction of* 5-*Ethyl*-5-1′-*methylthiobarbituric Acid and* 4-*Amino*-1 : 2 : 3 : 4-*tetrahydro*-1 : 3-*dimethyl*-5-*nitroso*-2 : 4-*dioxopyrimidine*.—A mixture of the thiobarbituric acid (2·2 g.) and the pyrimidine (1·62 g.) with anhydrous sodium acetate (0·3 g.) was heated at 200—204° until the reaction ceased (3 min.). The melt was triturated with ether (50 ml.), and the remaining solid after trituration with methanol (30 ml.) was extracted with 0·5N-sodium hydroxide, the extract acidified with glacial acetic acid, and the precipitate recrystallised from ethanol, forming needles (0·1 g.), m. p. 334°. Analyses were not consistent with 5-ethyl-3 : 4 : 5 : 6-tetrahydro-5-1′-methylbutyl-4 : 6-dioxopyrimidine. The methanol solution was evaporated to dryness and the residue extracted with chloroform (200 ml.), leaving a brown resin (0·6 g.). 8-Thiatheophylline (0·1 g.) was isolated from the resinous impurities in the chloroform solution by passing it through alumina, evaporating the solution to dryness, and subliming the residue at 140°/1 mm. Concentration of the ether solution first yielded crude 8-thiatheophylline which, after sublimation, had m. p. 184° (0·3 g.), and finally, unchanged thiobarbituric acid (0·45 g.) which was identified by mixed m. p. (157°) and analysis (Found: S, 13·0. Calc. for $C_{11}H_{18}O_2N_2S$: S, 13·2%).

*Preparation of* 2-*Amino*-6-*hydroxy*-8-*thiapurine from* 2 : 6-*Diamino*-8-*thiapurine*.—2 : 6-Diamino-8-thiapurine (2 g.), boiled for 45 min. with concentrated hydrochloric (10 ml.) and water (10 ml.), gave, on cooling, a precipitate which was collected and dissolved in 0·5N-sodium hydroxide (50 ml.). Aqueous 2N-acetic acid (*ca.* 2·3 ml.) was cautiously stirred in and a brown amorphous precipitate removed. The clear filtrate, acidified (litmus) with acetic acid, gave a yellow amorphous precipitate which, crystallised from 2N-hydrochloric acid, gave buff-coloured prisms (0·8 g.), m. p. 380° (decomp.), of 2-*amino*-6-*hydroxy*-8-*thiapurine hydrochloride* (Found: C, 22·9; H, 2·2; N, 32·3; S, 14·5; Cl, 16·0. $C_4H_3ON_5S,HCl,\frac{1}{2}H_2O$ requires C, 22·4; H, 2·3; N, 32·6; S, 14·9; Cl, 16·5%). Identity with the compound synthesised from 2 : 4 : 5-triamino-6-hydroxypyrimidine (see below) was established by mixed m. p. and ultraviolet absorption spectrum. In 0·1N-hydrochloric acid $\lambda_{max.}$ was 309 mμ (ε 9700); $\lambda_{min.}$ 265 (ε 765).

*Synthesis of* 8-*Thiapurines from* 4 : 5-*Diaminopyrimidines and Thionyl Chloride*.—2 : 4 : 5 : 6-Tetra-aminopyrimidine hydrogen sulphite (1 g.) was dispersed in thionyl chloride (30 ml.), boiled for 1½ hr., then cooled, the solid was collected, washed with ether, and triturated with warm 2N-ammonia, and the solid crystallised from water, yielding yellow needles, m. p. 355°, of 2 : 6-diamino-8-thiapurine (Found: C, 28·3; H, 2·6; N, 49·7; S, 18·5%).

4 : 5-Diamino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-2 : 4-dioxopyrimidine and thionyl chloride was boiled for 20 min., the solid dissolving completely. After evaporation to dryness, trituration of the residue with 2N-ammonia, and recrystallisation from water gave needles (0·4 g.), m. p. 154°, of 8-thiatheophylline, identified by mixed m. p. with the product made according to Blicke and Godt.[5]

4-Amino-2 : 3-dihydro-6-hydroxy-3-methyl-5-nitroso-2-oxopyrimidine (1 g.), suspended in water (6 ml.) and 2N-ammonia (2 ml.), was stirred with addition of sodium dithionite until all the nitroso-compound had disappeared; spontaneous warming to about 45° occurred. Cooling, filtration, and recrystallisation of the solid from water yielded 4 : 5-diamino-2 : 3-dihydro-6-hydroxy-3-methyl-2-oxopyrimidine (0·5 g.). The diamine was dispersed in thionyl chloride (20 ml.), the mixture boiled for 4½ hr., then cooled, and the solid collected, extracted with 20%

aqueous ammonia (20 ml.), and acidified with acetic acid. The dried precipitate sublimed at 150°/1 mm., yielding 2 : 3-dihydro-6-hydroxy-3-methyl-2-oxo-8-thiapurine (0·16 g.), m. p. 218°; recrystallised from water, this had m. p. 219° (0·10 g.) (Found: C, 32·3; H, 2·4; N, 30·3; S, 16·9%).

2 : 4 : 5-Triamino-6-hydroxypyrimidine (0·45 g.) and thionyl chloride (9 ml.) were boiled for 6½ hr., the whole evaporated to dryness, and the residue recrystallised from 2N-hydrochloric acid in buff-coloured prisms of 2-amino-6-hydroxy-8-thiapurine hydrochloride, m. p. (decomp.) 380° (Found: C, 22·5; H, 2·5; N, 32·8; S, 14·8; Cl, 16·2%).

4 : 5-Diamino-2 : 6-dihydroxypyrimidine (0·5 g.) and thionyl chloride (15 ml.) were boiled for 7½ hr., all the solids dissolving. After evaporation to dryness the residue was washed with water and recrystallised to purity (indicated by paper chromatography) from water, yielding stout buff prisms (0·2 g.) of 2 : 6-dihydroxy-8-thiapurine (Found: C, 28·4; H, 1·5; N, 33·1; S, 18·5. Calc. for $C_5H_2O_2N_4S$: C, 28·2; H, 1·2; N, 32·9; S, 18·8%).

4 : 5 : 6-Triaminopyrimidine hydrogen sulphite (0·8 g.) and thionyl chloride (30 ml.) were boiled together for 2 hr. After cooling, the precipitate was collected, washed with ether and very dilute ammonia solution, and recrystallised from water in buff needles (0·30 g.), m. p. 248°, of 6-amino-8-thiapurine (Found: C, 31·8; H, 2·0; N, 45·2; S, 20·4. Calc. for $C_5H_3N_5S$: C, 31·4; H, 2·0; N, 45·7; S, 20·9%).

I am much indebted to Dr. P. D. Lawley for determination of ultraviolet spectra and to Dr. S. F. D. Orr for examination of infrared spectra, also to Mr. D. Manners for technical assistance.

This investigation has been supported by grants to this Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

Chester Beatty Research Institute: The Royal Cancer Hospital,
Fulham Road, London, S.W.3. [*Received, August 29th*, 1956.]

---

## 157. *The Ionic Dissociation and Reactivity of Some Arylmethyl Chlorides.*

By S. F. Mason.

The anomalous variation of the free energy of ionisation of the triarylmethyl chlorides in liquid sulphur dioxide with the delocalisation energy of the carbonium ions produced has been shown to be due to concomitant variations in the electron interaction and solvation energies. The relative free energies of activation for the solvolysis of a series of arylmethyl chlorides are found to be governed by the electron interaction and solvation energies of the corresponding carbonium ions, as well as their delocalisation energies.

It has been shown[1] that a regular relation exists between the ionisation constants of a series of triarylmethyl chlorides, measured in sulphur dioxide at 0°, and the delocalisation energy, calculated by the Hückel approximation, of the triarylmethyl ions produced by the ionisation. The plot of the free energy of ionisation, $\Delta G_1$, against $E_D\beta^{-1}$, the delocalisation energy of the carbonium ion expressed in terms of the carbon–carbon resonance integral, $\beta$, is given in Fig. 1*A* for the compounds in which the steric hindrance is constant, *i.e.*, there are *o*–*o'*-contacts only. The plot of $\Delta G_1$ against $E_D\beta^{-1}$ is curved, and the averaged slope suggests that $\beta$ has a value of about −40 kcal./mole. The free energy of dissociation, $\Delta G_2$, of the hexa-arylethanes to triarylmethyl radicals in benzene solution at 25° is also a smooth function of $E_D\beta^{-1}$ (Fig. 1*B* and *C*), the delocalisation energy of a radical and of the corresponding carbonium ion being identical according to the Hückel approximation. For compounds in which again the steric effect is constant (*o*–*o'*-contacts between the aryl groups in the ethanes and the radicals), two distinct curves

[1] Streitwieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5288.

are obtained, one for the series of compounds in which the aryl groups are phenyl or *p*-diphenylyl residues (Fig. 1*B*), and the other for the series in which the groups are phenyl or 2-naphthyl residues (Fig. 1*C*), the averaged slopes of these curves giving β about −25 kcal./mole.

The equilibria of triarylmethyl systems are not adequately explained on the basis of the Hückel approximation, which, if valid, would require the relations of Fig. 1 to be linear with slopes giving β the value appropriate to the approximation, namely,[2] −20 kcal./mole. In calculating π-electron energies by the Hückel method, no account is taken of electron interaction, overlap, changes in compressional energy, and, in the present case, the non-planarity of the conjugated system. The effects of the last three factors on a given triarylmethyl radical and the corresponding ion are the same, so that they cannot account for the different apparent β values obtained from Fig. 1*A* and Figs. 1*B* and *C*.

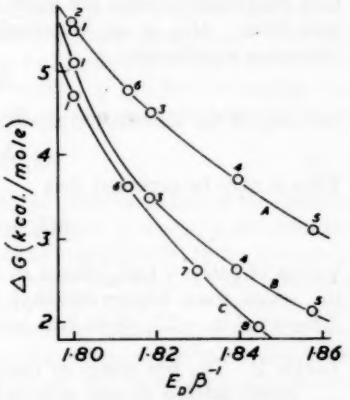



FIG. 1. *A, Variation of the free energy of ionisation of triarylmethyl chlorides with the delocalisation energy of the carbonium ion produced. B and C, Variation of the free energy of dissociation of hexa-arylethanes with the delocalisation energy of the radicals produced. The ordinate of B has been raised, and that of C lowered, by 0·2 kcal./mole. The numbers refer to the substances in Table* 1.

However, it has been shown [3] by a simplified self-consistent method, with the Hückel molecular orbitals as a base, that an odd alternant hydrocarbon radical and the corresponding carbonium ion possess different resonance energies, owing to differing electronic interactions. The resonance energy, $E_R$, of an arylmethyl radical or ion, additional to that of the aromatic nucleus, is given [3] by the expression:

$$E_R = E_D \pm E_C + E_B \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

the second term on the right-hand side of equation (1) being positive for the radical and negative for the carbonium ion. The first term, $E_D$, is due to the delocalisation of the π-electrons over a σ-core field which is more extensive in the arylmethyl system than in the aromatic nucleus, and it is equivalent to the Hückel delocalisation energy:

$$E_D = 2[\textstyle\sum'_{r>s} P_{rs(ArMe)} - \sum'_{r>s} P_{rs(Nuc)}]\beta \quad . \quad . \quad . \quad . \quad (2)$$

where $P_{rs}$ is the mobile bond order between the atoms r and s, the sums $\sum'$ being taken over adjacent atoms, and ArMe refers to the arylmethyl radical or ion and Nuc to the corresponding aromatic nucleus. The second term, $E_C$, arises from the lower probability that a pair of electrons shall be situated on a given atom in the delocalised than in the fixed-bond state of the arylmethyl system:

$$E_C = \tfrac{1}{2}\textstyle\sum_{s>t}^{st} C_{or}^2\, C_{ot}^2(\gamma_{11} - \gamma_{rt}) \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $C_{ur}$ is the coefficient of the non-bonding molecular orbital at atom r, the sum $\sum^{st}$ is taken over starred atoms, and $\gamma_{rt}$ is the electron repulsion integral between atoms r and t.

[2] Coulson, "Valence," Oxford Univ. Press, 1952, p. 240.
[3] Brickstock and Pople, *Trans. Faraday Soc.*, 1954, **50**, 901.

The third term, $E_B$, is due to the smaller probability that pairs of electrons shall be found on neighbouring atoms in the arylmethyl system than in the aromatic nucleus:

$$E_B = \tfrac{1}{2}\left[\sum_r^{st}\sum_s^{un} P_{rs}^2(\gamma_{12} - \gamma_{rs})_{ArMe} - \sum_{r>s} P_{rs}^2(\gamma_{12} - \gamma_{rs})_{Nuc}\right] \quad . \quad . \quad (4)$$

where $\sum^{un}$ refers to summation over unstarred atoms, and the other symbols have their former significance.

Evaluation of $E_D$ and, particularly, $E_B$ for the triarylmethyl radicals and ions is laborious, though an approximate value for $E_D$ is readily found [4] from the coefficient of the non-bonding molecular orbital at the exocyclic atom. However, $E_C$, which represents one-half of the energy difference between a radical and the corresponding carbonium ion, can be calculated from the coefficients of the non-bonding molecular orbital and repulsion integrals evaluated by the point-charge approximation.[3] Values of $E_C$ (Table 1) indicate that triarylmethyl ions are more stable than the corresponding radical by some 60—70 kcal./mole. $\Delta G_1$ is an empirical measure of the free-energy change of the overall ionisation equilibrium:

$$Ar_3CCl \rightleftharpoons Ar_3C^+ + Cl^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

and $\Delta G_2$ of the dissociation equilibrium:

$$Ar_3C{-}CAr_3 \rightleftharpoons 2Ar_3C\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Thus it may be expected that

$$\Delta G_1 - \tfrac{1}{2}\Delta G_2 = -2E_C + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Values of $(\Delta G_1 - \frac{1}{2}\Delta G_2)$ listed in Table 1 show that the differential in this quantity in the series from triphenylmethyl to tris-*p*-diphenylylmethyl (0·88 kcal./mole) and the differential in $-2E_C$ (8·89 kcal./mole) agree in sign but not in magnitude.

TABLE 1. *The free energy of ionisation of the triarylmethyl chlorides* RR′R″CCl ($\Delta G_1$) *in liquid sulphur dioxide at* 0—0·12° ; *the free energy of dissociation of the hexa-arylethanes* $(RR'R''C\cdot)_2$ ($\Delta G_2$) *in benzene at* 25°; *the delocalisation energy* ($E_D\beta^{-1}$) *of the corresponding carbonium ion and radical*; *the charge dispersal energy difference* ($2E_C$) *between the latter*; *and the summed squares of the Hückel charges* ($\sum_r q_r^2$) *of the carbonium ion. Energies are given in kcal./mole.*

| | Substituents [a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. | R | R′ | R″ | $\Delta G_1$ | $\Delta G_2$ | $(\Delta G_1 - \frac{1}{2}\Delta G_2)$ | $E_D\beta^{-1}$ | $2E_C$ [b] | $\Sigma_r q_r^2$ [c] |
| 1 | Ph | Ph | Ph | 5·48 [b] | 4·90 [d] | 3·03 | 1·8004 [e] | 61·89 | 0·1482 |
| 2 | *m*-$C_6H_4Ph$ | ,, | ,, | 5·64 [b] | — | — | 1·7990 [e] | — | — |
| 3 | *p*-$C_6H_4Ph$ | ,, | ,, | 4·53 [b] | 3·27 [e] | 2·89 | 1·8184 [e] | 65·16 | 0·1333 |
| 4 | ,, | *p*-$C_6H_4Ph$ | ,, | 3·72 [b] | 2·45 [f] | 2·50 | 1·8396 [e] | 68·13 | 0·1209 |
| 5 | ,, | ,, | *p*-$C_6H_4Ph$ | 3·13 [b] | 1·96 [f] | 2·15 | 1·8578 [e] | 70·78 | 0·1096 |
| 6 | 2-$C_{10}H_7$ | Ph | Ph | 4·80 [e] | 3·84 [f] | 2·88 | 1·8134 [e] | 63·54 | 0·1411 |
| 7 | ,, | 2-$C_{10}H_7$ | ,, | — | 2·85 [f] | — | 1·830 [g] | — | — |
| 8 | ,, | ,, | 2-$C_{10}H_7$ | — | 2·15 [f] | — | 1·845 [g] | — | — |

[a] Data for compounds containing a 1-naphthyl group or two or more *m*-diphenylyl groups are omitted from the Table as the steric factors in these compounds differ from those of the compounds listed. [b] Lichtin and Leftin, *J. Phys. Chem.*, 1956, **60**, 164. [c] Ref. 1. [d] Calc. from the data of Muller and Muller-Rodloff, *Annalen*, 1935, **521**, 89. [e] Calc. from the data of Marvel, Mueller, and Ginsberg, *J. Amer. Chem. Soc.*, 1939, **61**, 2008. [f] Calc. from the data of Marvel, Shackleton, Himel, and Whitson, *ibid.*, 1942, **64**, 1824. [g] Calc. from the empirical relation, $-E_D\beta^{-1} = 2{\cdot}60 - 1{\cdot}45C_{ox}$, based on Dewar's theory.[4] [h] Calc. by Brickstock and Pople's method.[5] [i] Calc. from the coefficients of the N.B.M.O., obtained by the method of Longuet-Higgins (*J. Chem. Phys.*, 1950, **18**, 275).

The failure of equation (7) to hold quantitatively suggests that the resonance energy of a triarylmethyl ion, whilst rising steeply relatively to that of the corresponding radical in the series studied, is partly offset by another differential energy factor, such as that due to the solvation of the ions. The solvation energy of an ion can be divided into three

[4] Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3341.

main terms: [5] that due to cavity formation; that due to dielectric saturation in the primary solvation shell of the ion; and that due to the Born charging. The cavities formed in a solvent by a triarylmethyl ion and a chloride ion should not differ greatly from those formed by the corresponding undissociated triarylmethyl chloride, and the energy of cavity formation should not vary widely in the series. The positive charge on any one carbon atom of a triarylmethyl ion is small (the maximum charge is 0·308 in the present series), so that there may be no dielectric saturation in the primary solvation sheath of the ion. Should such saturation occur, the interaction energy between a triarylmethyl ion and solvent dipoles in the first co-ordination shell is given by the expression:

$$E_I = \sum_r \sum_s q_r ezze/d \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where $q_r$ is the fraction of a positive charge on atom r, and $d$ is the distance between that atom and the fractional charge, $z$, of the dipole of a solvent molecule in the first solvation shell, $e$ being the electronic charge. It may be expected that $\sum_s ze^2/d$ does not vary greatly from one charged centre to another in a triarylmethyl ion, or, more particularly, from one ion to another, and since $\sum_r q_r$ is unity for each carbonium ion, $E_I$ should not be a differential energy term in the present series. However, the free energy of the Born charging of a triarylmethyl carbonium ion, $\Delta G_S$, given by equation (9), should vary considerably from one ion to another:

$$\Delta G_S = -\sum_s q_r^2 e^2 (1 - 1/D)/2R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

where $D$ is the dieletric constant of the solvent, and $R$ is the effective radius of the charged centre, atom r, in the carbonium ion. If a Hückel distribution of charge is assumed for the carbonium ions, $\sum_r q_r^2$ varies from 0·148 for the triphenylmethyl to 0·110 for the tris-*p*-diphenylylmethyl ion (Table 1). Thus the solvation energy due to the Born charging falls as the resonance energy of the carbonium ion, relatively to that of the corresponding radical, rises in the series. Moreover, the changes in solvation and resonance energy are proportional one to the other in the series, $\sum_r q_r^2$, the variable parameter in the equation (9) for the Born charging energy, being a smooth, nearly linear, function of $E_C$, the charge dispersal energy (Fig. 2*A*). After allowance for changes in the solvation energy, equation (7) becomes:

$$\Delta G_1 - \tfrac{1}{2}\Delta G_2 = \Delta G_S - 2E_C + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

and it is found that the experimental data for $(\Delta G_1 - \frac{1}{2}\Delta G_2)$ are accounted for quantitatively by equation (10) if $R$ is given the value of $0{\cdot}8(1 - 1/D)$ Å. When $D$ is identified with the bulk dielectric constant (15·35) of liquid sulphur dioxide at 0°, the value for $R$ becomes 0·75 Å, which is close to the ionic radius of carbon [6] (0·58 Å) but larger. In calculating solvation energies due to the Born charging it is necessary to employ effective radii larger than the ionic radii of the ions solvated in order to allow for the polarised solvent molecules in the primary co-ordination shell.[5] Dielectric saturation may not occur in the ions of the present series (see above), but, for carbonium ions, it is necessary to allow also for substituents attached to the positively charged carbon atom.[6]

The variation of the ionisation constants of the triarylmethyl chlorides with the energy parameters discussed above has a bearing on their reactivities. It has been argued [7] that conjugated carbonium ions, such as allyl and benzyl, cannot have a resonance energy since allyl and benzyl chloride are solvolysed in formic acid only $10^2$—$10^4$ times as fast as primary alkyl chlorides,[8,9] whilst if the allyl and benzyl carbonium ions are stabilised by the Hückel delocalisation energy (*ca.* 15 kcal./mole) they should be solvolysed some $10^{10}$—$10^{13}$ times as fast. The self-consistent field treatment [3] suggests that allyl and benzyl ions

[5] Eley and Evans, *Trans. Faraday Soc.*, 1938, **34**, 1093; Latimer, Pitzer, and Slansky, *J. Chem. Phys.*, 1939, **7**, 108; Pearson, *ibid.*, 1952, **20**, 1478.
[6] Franklin, *Trans. Faraday Soc.*, 1952, **48**, 443.
[7] Franklin and Lumpkin, *J. Chem. Phys.*, 1951, **19**, 1073.
[8] Bateman and Hughes, *J.*, 1940, 945.
[9] Evans and Hamann, *Trans. Faraday Soc.*, 1951, **47**, 25.

have much larger resonance energies (*ca.* 60 kcal./mole, Table 2), so that they might be expected to be solvolysed some $10^{44}$ times as fast as primary alkyl chlorides. However, the charge of a conjugated carbonium ion is delocalised, so that, by equation (9), such ions have a smaller solvation energy due to the Born charging than alkyl ions in the same solvent. For the benzyl ion $\sum_r q_r^2$ (equation 9) has the value of 0·387 (Table 3), whilst for an alkyl ion the value of this parameter is unity. Thus the resonance energy of a

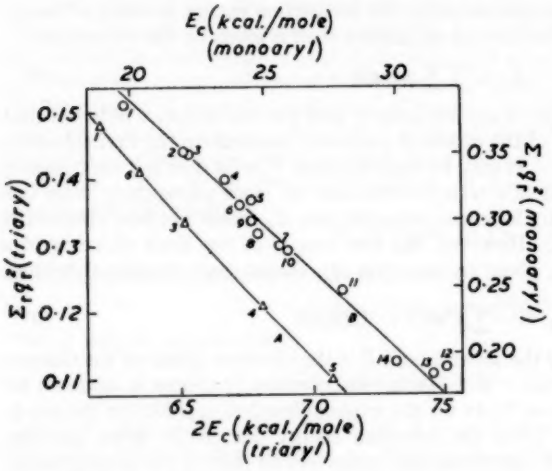



FIG. 2. *A, Variation of the difference in resonance energy between a triarylmethyl ion and the corresponding radical, $2E_C$, with the parameter, $\sum_r q_r^2$, governing the solvation energy of the carbonium ion due to the Born charging (numbers refer to the substances in Table* 1). *B, Variation of the charge dispersal energy, $E_C$, of monoarylmethyl ions with the solvation energy parameter, $\sum_r q_r^2$. (Numbers refer to the substances in Table* 3.)

conjugated carbonium ion compensates for its loss of Born charging solvation energy, which, in general, is proportional to $(1 - \sum_r q_r^2)$. On this basis it is found that if, as the data [8,9] suggest, the free energy of activation for the solvolysis of benzyl chloride in formic acid is some 5 kcal./mole lower than that of a primary alkyl chloride, the effective

TABLE 2. *The delocalisation ($E_D$), charge dispersal ($E_C$), and bond–bond interaction energy ($E_B$) of some conjugated carbonium ions* (in kcal./mole).

| Ion | $E_D$ [a] | $E_C$ [c] | $E_B$ [d] |
|---|---|---|---|
| Allyl | −45·6 [b] | 14·6 [b] | 0 |
| Benzyl | −39·7 | 19·8 [b] | −2·0 |
| 2-Naphthylmethyl | −41·0 | 22·3 | −3·3 |
| 1-Naphthylmethyl | −44·8 | 24·8 | −3·3 |
| 9-Anthrylmethyl | −52·4 | 30·0 | −8·9 |

[a] Calc. from equation (2) with $\beta = -55{\cdot}1$ kcal./mole (ref. 3). [b] Ref. 3. [c] Calc. from equation (3) with $\gamma_{11} = 242{\cdot}7$, $\gamma_{12} = 125{\cdot}9$ kcal./mole, and the point charge approximation values for larger distances. [d] Calc. from equation (4) with $\gamma_{12} = 168{\cdot}3$, $\gamma_{14}$ (*cis*) = 113·0 kcal./mole, and the point charge approximation values for larger distances.

radius of a charged centre in the benzyl ion ($R$, equation 9) is 1·77 Å, when $D$ is given the value of the bulk dielectric constant of formic acid (58·5 at 16°). A study of the ionisation constants of the triarylmethyl chlorides gave $R$ the value of 0·75 Å (see above). The larger value obtained for the benzyl ion may be due in part to the dielectric saturation of the solvent round the exocyclic atom, owing to the considerable charge (0·57), so that the effective radius for the Born charging is increased. However, the large value for $R$, in part at least, is apparent only, arising from the assumption (equation 9) that the separation of charge between the carbonium and the chloride ions is as complete in the solvolytic transition state of benzyl chloride as in the ionic equilibria of the triarylmethyl chlorides.

An analysis of the effect of added salt on the rates of solvolysis of alkyl and arylmethyl

halides in 90% aqueous acetone has shown [10] that the separation of charge in the transition state is not complete in these reactions, though the fractional positive charge is delocalised in the partly formed arylmethyl ion. For a degree of ionisation, $\alpha$, with the assumption

TABLE 3. *The logarithms of the rate constants for the reaction of the monoarylmethyl chlorides:* I, $S_N2$ *reaction with potassium iodide in acetone.* II, *Solvolysis in water* (6·1%)–*formic acid* (54·1%)–*dioxan* (39·8%). III, *Solvolysis in water* (5·8%)–*formic acid* (34%)–*dioxan* (60·2%). IV, *Solvolysis in moist formic acid* (0·38M *in water*). *The delocalisation energies* ($E_D\beta^{-1}$), *coefficient of the N.B.M.O. at the exocyclic atom* ($C_{ox}$), *charge dispersal energies* ($E_C$), *and the summed squares of the Hückel charges* ($\sum_r q_r^2$) *of the corresponding carbonium ions.*

| | | log $k$ (25°) | | | | | | $E_C$[f] | |
|---|---|---|---|---|---|---|---|---|---|
| No. | Aryl | I [a] | II [a] | III [a] | IV [b] | $C_{ox}$ | $E_D\beta^{-1}$ | (kcal./mole) | $\Sigma_r q_r^2$ |
| 1 | Phenyl | −3·19 | −7·61 | — | −6·94 | 0·756 | 0·722 [c] | 19·8 | 0·387 |
| 2 | 2-Phenanthryl | −2·91 | −7·13 | — | −5·55 | 0·737 | 0·74 [d] | 22·1 | 0·351 |
| 3 | 2-Naphthyl | −2·86 | −7·09 | — | −5·59 | 0·728 | 0·744 [e] | 22·3 | 0·350 |
| 4 | 2-Triphenylenyl | — | — | — | −5·43 | 0·728 | 0·74 [d] | 23·7 | 0·331 |
| 5 | 3-Phenanthryl | −2·85 | −6·45 | — | −4·80 | 0·714 | 0·76 [d] | 24·6 | 0·315 |
| 6 | 4-Phenanthryl | −2·51 | −5·77 | — | — | 0·700 | 0·78 [d] | 24·2 | 0·311 |
| 7 | 1-Phenanthryl | −2·58 | −6·55 | −7·50 | −4·77 | 0·680 | 0·80 [d] | 25·7 | 0·282 |
| 8 | 1-Naphthyl | −2·64 | −6·26 | −7·31 | −4·36 | 0·671 | 0·812 [e] | 24·8 | 0·290 |
| 9 | 9-Phenanthryl | −2·58 | −6·38 | −7·36 | −4·31 | 0·668 | 0·813 [e] | 24·6 | 0·297 |
| 10 | 3 : 4-Benzo-2-phenanthryl | −2·55 | −5·33 | −6·80 | — | 0·667 | 0·81 [d] | 26·0 | 0·278 |
| 11 | 2-Chrysenyl | — | — | — | −2·89 | 0·641 | 0·84 [d] | 28·0 | 0·247 |
| 12 | 3-Pyrenyl | −2·08 | −3·02 | −4·46 | — | 0·603 | 0·88 [d] | 31·9 | 0·190 |
| 13 | 1 : 2-Benz-10-anthryl | −1·56 | — | −4·35 | — | 0·560 | 0·92 [d] | 31·4 | 0·185 |
| 14 | 9-Anthryl | −1·42 | — | −4·16 | — | 0·535 | 0·951 [e] | 30·0 | 0·194 |

[a] Ref. 12 and Brandli, Dujardin, Fierens, Martin, and Planchon, *Helv. Chim. Acta*, 1956, **39**, 1501. [b] Ref. 11. [c] Calc. by the L.C.A.O. method without overlap. [d] Calc. from the empirical relation, $E_D\beta^{-1} = 1{\cdot}50 - 1{\cdot}03C_{ox}$, based on Dewar's theory.[4] [e] Wheland, *J. Amer. Chem. Soc.* 1941, **63**, 2025. [f] Calc. by the method of ref. 3.

that the delocalised charge follows the Hückel distribution in the partly formed arylmethyl, equation (9) becomes:

$$\Delta G_S = -\sum_r q_r^2\alpha^2e^2(1 - 1/D)2R \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

and since $1 > \alpha > 0$, effective radii calculated by equation (9) are too large. The incomplete ionisation of an arylmethyl chloride in a transition state has the effect of reducing both the solvation and the resonance energy of the carbonium ion, but not all of the terms contributing to the latter energy are reduced proportionately. Equations (2), (3), (4), and (11) suggest that a partly formed arylmethyl ion has a delocalisation energy proportional to $\alpha$, but solvation, $\Delta G_S$, and electron interaction energies, $E_C$ and $E_B$, proportional to $\alpha^2$. Thus the variation in the free energy of activation, $\Delta G^\ddagger$, in a series of arylmethyl chlorides for a given reaction should be given by the equation:

$$\Delta G^\ddagger = \alpha E_D + \alpha^2(\Delta G_S + E_B - E_C) + \text{Constant} \quad . \quad . \quad . \quad . \quad (12)$$

The logarithms of the rate constants of a series of arylmethyl chlorides have been correlated with the coefficient of the non-bonding molecular orbital at the exocyclic atom in the corresponding carbonium ion, a parameter proportional to the Hückel delocalisation energy,[4] for a number of reactions, examples of which are given in Fig. 3 and Table 3. The rate constants for the $S_N2$ reaction of the arylmethyl chlorides with potassium iodide in acetone give good correlation with the Hückel delocalisation energy expressed in terms of the carbon–carbon resonance integral, $E_D\beta^{-1}$ (Fig. 3*A*), but plots of the solvolyses in water–formic acid–dioxan (Fig. 3*B*) and in formic acid (Fig. 3*C*) involve scatter and give apparent $\beta$ values (*ca.* −40 and −60 kcal./mole respectively) much larger than the Hückel value [2] (−20 kcal./mole).

[10] Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979.

From equation (12) it is apparent that when $\alpha$ is small, as in the $S_N2$ reaction, the solvation and electron interaction terms, and their variations within the series of arylmethyl derivatives, are very small. Thus the delocalisation energy, $E_D$, remains the major variable in the series, and the relative rate constants of $S_N2$ reactions should give good correlation with $E_D$, as is found (Fig. 3*A*). However, when $\alpha$ approaches unity, as in $S_N1$ reactions, all of the energy terms on the right-hand side of equation (12) become important variables determining the relative free energies of activation in the series of arylmethyl chlorides. The electron interaction energies, $E_B$ and $E_C$, whilst showing a general trend towards larger values as the delocalisation energy, $E_D$, increases, are not smooth functions of $E_D$ (Tables 2 and 3), and $\sum_r q_r^2$, the parameter determining the solvation energy of a conjugated carbonium ion due to the Born charging, shows similarly only a general trend towards smaller values as $E_D$ increases (Table 3). However, changes in the

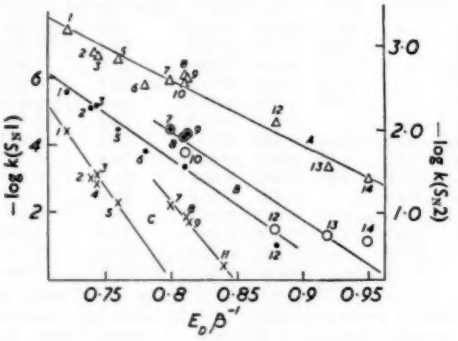



FIG. 3. *Relation between the delocalisation energies of the arylmethyl ions and the logarithms of the relative rate constants for the reaction of the arylmethyl chlorides.*

*A* (△) *Potassium iodide in acetone.*

*B* (●) *Solvolysis in water* (6·1%)*–formic acid* (54·1%)*–dioxan* (39·8%); (○) *solvolysis in water* (5·8%)*–formic acid* (34%)*–dioxan* (60·2%).

*C* (×) *Solvolysis in moist formic acid* (0·38M *in water*). (*Numbers refer to the compounds in Table* 3.)

charge dispersal energy, $E_C$, and the solvation energy, $\Delta G_S$, mutually compensate to some degree in the monoarylmethyl as in the triarylmethyl ions (see above), as $E_C$ and $\sum_r q_r^2$ are related in the monoarylmethyl series (Fig. 2*B*), though not so smoothly as in the triarylmethyl series (Fig. 2*A*). In particular, the 3-pyrenylmethyl ion has rather a large charge dispersal energy, $E_C$, in relation to its value of the solvation energy parameter, $\sum_r q_r^2$ (Fig. 2*B*, Table 3), a divergence perhaps connected with the absence of charge on a starred atom in this ion. The divergence suggests that 3-pyrenylmethyl chloride should be a particularly reactive compound, as is found (Fig. 3*B*, Table 3).

The partial compensation between the charge dispersal, $E_C$, and solvation energy, $\Delta G_S$, has the effect of leaving the bond–bond interaction term, $E_B$, as an important source of deviation from correlations between the delocalisation energy, $E_D$, and the relative rate constants for the $S_N1$ reactions of a series of arylmethyl chlorides. The calculated values of the bond–bond interaction term, $E_B$, show (Table 2) that, whilst it is small, $E_B$ increases rapidly with the number of condensed rings in the arylmethyl system, owing to the increasing number of electrons delocalised over the exocyclic bond on carbonium-ion formation, and that the value of $E_B$ depends on the particular aromatic nucleus substituted, and not on the position at which the exocyclic methyl group is attached, in the case of naphthalene and perhaps more generally. Such properties of the bond–bond interaction term, $E_B$, suggest, from equation (12), that, in correlations between $E_D$ and the relative rate constants for the $S_N1$ reactions of a series of arylmethyl chlorides, the larger polycyclic derivatives should be more reactive than smaller congeners with the same delocalisation energy, and that, of the derivatives of a given aromatic nucleus, notably naphthalene and perhaps other nuclei, those with the smaller delocalisation energies should react faster, and those with the larger delocalisation energies more slowly, than their $E_D$ values would indicate. The relative solvolysis rates [11,12] of the naphthylmethyl and phenanthrylmethyl chlorides

[11] Dewar and Sampson, *J.*, 1956, 2789; 1957, 2946, 2952.
[12] Fierens, Hannaert, Rysselberge, and Martin, *Helv. Chim. Acta*, 1955, **38**, 2009.

in a given medium illustrate the latter point (Figs. 3*B* and *C*, Table 3), but the derivatives with the larger delocalisation energies are all *peri*-compounds, and it is possible that there is steric hindrance between the methyl and *peri*-CH groups in the carbonium ion.[11] Such a steric effect is not evident in the $S_N2$ reaction with potassium iodide in acetone, even for the *meso*-compounds (Fig. 3*A*, Table 3), though gross hindrance, as in the case of the *peri*-2-aryl-2-chloropropanes, does lead to marked retardation of solvolysis.[11] In general, the tetracyclic arylmethyl chlorides are solvolysed[11,12,13] faster than might be expected from the values of their delocalisation energies (Figs. 3*B* and *C*, Table 3). In particular, 2-triphenylenylmethyl chloride is solvolysed some 40% faster than 2-naphthylmethyl chloride in formic acid,[11] the corresponding carbonium ions having the same delocalisation energies, and 3 : 4-benzo-2-phenanthrylmethyl chloride is solvolysed 3—16 times as rapidly as 1-naphthyl- and 9-phenanthryl-methyl chloride in water–formic acid–dioxan mixtures,[12,13] the corresponding carbonium ions having very similar delocalisation energies (Table 3). However, 3 : 4-benzophenanthrene is an overcrowded nucleus, and the non-planarity of the system[14] may increase the reactivity of the 2-chloromethyl derivative by relieving *peri* steric hindrance in the carbonium ion.

It may be noted that the total resonance energies ($E_R$, equation 1) of the monoarylmethyl ions increase with the delocalisation energy components expressed in terms of the carbon–carbon resonance integral, $E_D\beta^{-1}$, according to a general trend which gives β the approximate apparent value of −120 kcal./mole (Table 2). The apparent β values obtained from correlation of $E_D\beta^{-1}$ with the relative rates of reaction of the arylmethyl

TABLE 4. *Logarithms of the probability factors* (log *PZ*) *for the reactions*: (a) *Of arylmethyl chlorides, as follows*: I, $S_N2$ *reaction with potassium iodide in acetone*; II, *solvolysis in water* (6·1%)–*formic acid* (54·1%)–*dioxan* (39·8%); III, *solvolysis in water* (5·8%)–*formic acid* (34%)–*dioxan* (80·2%); IV, *solvolysis in water* (20·5%)–*dioxan* (79·5%); V, *solvolysis in water* (49·3%)–*dioxan* (50·7%). (b) *Of* 1-*arylethyl chlorides, as follows*: VI, *Solvolysis in water* (20%)–*acetone* (80%); VII, *solvolysis in water* (10%)–*acetone* (90%). *Also the summed squares of the Hückel charges* ($\sum_r q_r^2$) *of the corresponding carbonium ions.*

| | | log *PZ* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. | Aryl | I [a] | II [a] | III [a] | IV [a] | V [a] | VI [b] | VII [b] | $\sum_r q_r^2$ |
| 1 | Phenyl | 10·07 | 8·61 | — | 7·02 | 8·26 | 10·1 | — | 0·387 |
| 2 | 2-Phenanthryl | 9·94 | 10·80 | — | — | — | 11·3 | — | 0·351 |
| 3 | 2-Naphthyl | 9·42 | 10·86 | — | — | — | 11·3 | — | 0·350 |
| 4 | 4-Diphenylyl | — | — | — | — | — | 11·2 | — | 0·319 |
| 5 | 2-Fluorenyl | — | — | — | — | — | 11·8 | 10·2 | 0·319 |
| 6 | 3-Phenanthryl | 9·94 | 10·51 | — | 9·38 | 10·20 | 11·7 | — | 0·315 |
| 7 | 4-Phenanthryl | 10·84 | 12·88 | — | — | — | — | — | 0·311 |
| 8 | 2-Anthryl | — | — | — | — | — | — | 10·2 | 0·310 |
| 9 | 9-Phenanthryl | 10·79 | 11·82 | 10·04 | 8·72 | 11·84 | 11·8 | — | 0·297 |
| 10 | 1-Naphthyl | 11·26 | 11·77 | 9·67 | 8·29 | 10·45 | 11·4 | — | 0·290 |
| 11 | 1-Phenanthryl | 10·79 | 13·07 | 10·08 | — | — | — | — | 0·282 |
| 12 | 3 : 4-Benzo-2-phenanthryl | 11·38 | 10·03 | 11·81 | 10·68 | 14·27 | — | — | 0·278 |
| 13 | 1-Anthryl | — | — | — | — | — | — | 10·4 | 0·248 |
| 14 | 2-Chrysenyl | — | — | — | — | — | 12·1 | 10·5 | 0·247 |
| 15 | 9-Anthryl | 10·55 | — | 3·35 | 11·18 | — | — | 9·5 | 0·194 |
| 16 | 3-Pyrenyl | 10·42 | — | 8·61 | — | — | — | 10·2 | 0·190 |
| 17 | 1 : 2-Benz-10-anthryl | 11·27 | — | 7·55 | 10·61 | 13·89 | — | — | 0·185 |

[a] Refs. 12, 13, and 16. [b] Berliner and Shieh, *J. Amer. Chem. Soc.*, 1957, **79**, 3849.

chlorides are smaller (*ca.* −60 kcal./mole for the solvolysis in moist formic acid, *ca.* −40 kcal./mole for solvolysis in water–formic acid–dioxan, and *ca.* −10 kcal./mole for reaction with potassium iodide in acetone), illustrating the effects of the incomplete separation of charge between the carbonium and the chloride ion in the transition state (equation 12),

[13] Brandli, Dujardin, Fierens, Martin, and Planchon, *ibid.*, 1956, **39**, 1501.
[14] Herbstein and Schmidt, *J.*, 1954, 3302.

and the decrease in the solvation energy of a carbonium ion with increasing resonance energy (equation 11, Tables 2 and 3).

The importance of the solvation energy of the carbonium ion as a determinant of the reactivity of arylmethyl chlorides is shown by the relative values of the pre-exponential factors for the various reactions of these compounds (Fig. 4, Table 4). The solvation energy due to the Born charging, $\Delta G_S$, is the only free-energy term on the right-hand side of equation (12), the components of the resonance energy being internal-energy terms. Thus the relative entropies of activation, $\Delta S^{\ddagger}$, of arylmethyl chlorides for a given reaction may be equated to the relative entropies of the solvation of the carbonium ions due to the

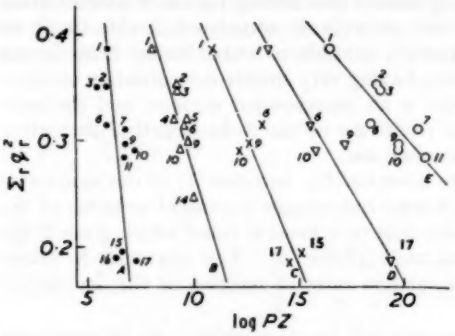



FIG. 4. *Relations between* $\sum_r q_r^2$, *the parameter governing the entropy of solvation of the carbonium ions due to the Born charging, and the pre-exponential factor,* log *PZ.*

*A* (●) $S_N2$ *reaction of arylmethyl chlorides with potassium iodide in acetone.*

*B* (△) *Solvolysis of 1-arylethyl chlorides in* 80% *acetone.*

*C* (×) *Solvolysis of arylmethyl chlorides in water* (20·5%)–*dioxan* (79·5%).

*D* (▽) *Solvolysis of arylmethyl chlorides in water* (49·3%)–*dioxan* (50·7%).

*E* (○) *Solvolysis of arylmethyl chlorides in water* (6·1%)–*formic acid* (54·1%)–*dioxan* (39·8%).

(*Numbers refer to the compounds in Table* 4.)

Born charging, which are given by the derivative of the right-hand side of equation (11) with respect to temperature:

$$\Delta S^{\ddagger} = \sum_r q_r^2 \alpha^2 e^2 (\mathrm{d} \ln D/\mathrm{d}T)/2RD + \text{Constant} \quad . \quad . \quad . \quad . \quad (13)$$

It is found that for five (Fig. 4) of the seven reactions for which information is available (Table 4) the pre-exponential factor, log $PZ$, increases as the Born charging parameter, $\sum_r q_r^2$, decreases, in conformity with equation (13), since (d ln $D$/d$T$) is invariably a negative quantity.[15] Moreover, log $PZ$ varies more widely with $\sum_r q_r^2$ the greater the ionising power of the reaction medium (Fig. 4), that is, the larger the degree of ionisation in the transition state, $\alpha$, again as equation (13) requires. From the slope of the relation between log $PZ$ and $\sum_r q_r^2$ for a given reaction medium a value may be obtained for $R/\alpha^2$, the ratio of the effective radius of a charged centre in a carbonium ion to the square of the separation of charge in the transition state. The temperature coefficients of the dielectric constants of mixed solvents are uncertain, but acetone and water, and presumably their mixtures, have the same value [15] for d ln $D$/d$T$, namely, $-4{\cdot}63 \times 10^{-3}$. By using this value it is found from the observed pre-exponential factors for the solvolysis of the 1-arylethyl chlorides in 80% acetone (Fig. 4*B*, Table 4) by equation (13) that $R/\alpha^2$ has the value of 0·4 Å. This value is too small, but it may be of the correct order of magnitude as it has been shown [10] for the solvolysis of *tert.*-butyl bromide in 90% acetone that the degree of ionisation in the transition state is approximately 0·5.

The pre-exponential factors for the reactions of 3 : 4-benzo-2-phenanthrylmethyl chloride, in which the aromatic nucleus is non-planar,[14] do not fit the observed correlations (Fig. 4) at all well, and those for the solvolysis of the 1-arylethyl chlorides in 90% acetone and arylmethyl chlorides in water (5·8%)–formic acid (34%)–dioxan (60·2%) show no obvious correlation with the Born charging parameter of the carbonium ions, $\sum_r q_r^2$ (Table 4). In the last series, for the most part, the more reactive members, which have the smaller $\sum_r q_r^2$ values, have the smaller log $PZ$ factors (Table 4), in apparent contradiction to equation (13). However, it has been suggested [11,16] that the more reactive arylmethyl

[15] Pearson, *J. Chem. Phys.*, 1952, **20**, 1478.
[16] Fierens and Berkowitch, *Tetrahedron*, 1957, **1**, 129.

chlorides are ionised more completely in the transition state than their less reactive analogues in reaction media of low ionising power. Such a change of mechanism, an increase in $\alpha$ when $\sum_r q_r^2$ is small, would lead (equation 13) to smaller pre-exponential factors for the solvolysis of the more reactive arylmethyl chlorides in these media.

The author is indebted to Dr. H. O. Pritchard for the Hückel coefficients and energy levels of the 9-anthrylmethyl radical.

THE UNIVERSITY, EXETER.

[*Received, May 20th*, 1957; *revised, August 19th*, 1957.]

---

## 158. *The Reaction of Ninhydrin with Cyclic α-Imino-acids.*

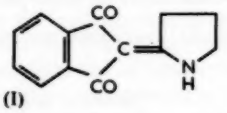
By A. W. JOHNSON and D. J. MCCALDIN.

Structures are proposed for the yellow and the purple condensation products from ninhydrin and the cyclic α-imino-carboxylic acids. Ring size is shown to have a marked influence on the course of the reaction. The purple condensation products are also obtained from ninhydrin and the cyclic bases and the mechanism of these condensations, which resembles that of the oxidative decarboxylation of α-amino-acids, is discussed.

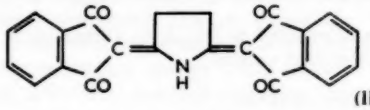
IT has been recognised for many years that, whereas most of the common α-amino-acids give purple colours with ninhydrin, proline and hydroxyproline give yellow colours.[1] When this reaction is used for identifications after chromatography on paper, it is sometimes observed that the yellow proline spot has a purple fringe, especially if the colour has been developed at temperatures rather higher than usual; and indeed, after prolonged heating, the yellow colour may be completely transformed into purple. The chemistry of these coloured proline condensation products was studied originally by Grassmann and Arnim [2] who suggested that their formation might be used as the basis for estimation of proline and hydroxyproline. Moore and Stein [3] realised that the cyclic α-imino-acids were anomalous in the method they developed for the photometric determination of α-amino-acids with ninhydrin. However, a modified procedure for the estimation of proline by means of ninhydrin was worked out in detail later by Chinard [4] who also showed that ornithine, lysine, and hydroxylysine gave comparable results, probably because of initial cyclisations to α-imino-acids. Chinard's method was again modified by later workers [5] with the result that details for the estimation of all the naturally occurring cyclic α-imino-acids, on the basis of the absorption spectra of the colours given with ninhydrin, are now available. In the case of proline, for example, a yellow colour ($\lambda_{max.}$ 350 mμ) is formed with ninhydrin in acetic acid at room temperature whereas a reddish-purple colour ($\lambda_{max.}$ 515 mμ) is formed with the same reagent at 100° in 35 minutes. If the latter reaction is carried out in neutral solution the resulting compound shows maximum absorption at 550 mμ, and it was this coloured product which was investigated chemically by Grassmann and Arnim.[2] They advanced structures (I) and (II) respectively for the yellow and the purple product and showed that the former was intermediate in the formation of the latter. These formulæ, which have been accepted by later workers,[5] were derived largely by analogy with the structures then proposed for compounds of the isatin-blue series, which are derived from pipecolic acid, proline, and related compounds by condensation with two equivalents of isatin.

[1] Abderhalden and Schmidt, *Z. physiol. Chem.*, 1911, **72**, 37.
[2] Grassmann and Arnim, *Annalen*, 1934, **509**, 288; 1935, **519**, 192.
[3] Moore and Stein, *J. Biol. Chem.*, 1948, **176**, 367.
[4] Chinard, *ibid.*, 1952, **199**, 91; see also Weisiger, *ibid.*, 1950, **186**, 591; Stein and Moore, *ibid.*, 1951, **190**, 103; Touster, *J. Amer. Chem. Soc.*, 1951, **73**, 491.
[5] Troll *et al.*, *J. Biol. Chem.*, 1953, **200**, 804; 1955, **215**, 655; Schweet, *ibid.*, 1954, **208**, 603; Piez, Irreverre, and Wolff, *ibid.*, 1956, **223**, 687.

In a recent paper,[6] we showed that the structure of the condensation product from isatin and proline was (III), and it seemed to us *a priori* that the purple ninhydrin products would be of a similar type. Proline reacts readily with ninhydrin in alcoholic solution, to

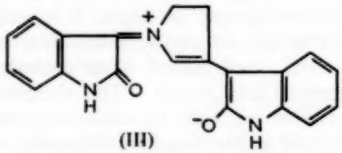


(I)

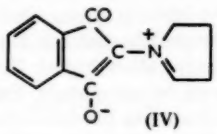


(II)

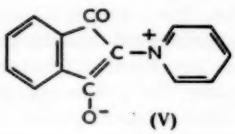
give a crystalline golden-yellow condensation product which we consider to be the enol betaine (IV) and indeed its colour, spectra, and other physical and chemical properties closely resemble those of the enol betaines (*e.g.*, V) described by Stafford.[7] The related compound from hydroxyproline and ninhydrin has also been prepared. The infrared spectrum of compound (IV) shows no band corresponding to a free imino-group, and thus structures such as (I) can be discounted. On the basis of structure (IV) for the yellow intermediate and (III) for the isatin–proline condensation product, we now formulate the purple-red condensation product from ninhydrin and proline as (VI), and the properties of this compound, especially the ultraviolet and visible absorption spectrum, are similar to those of the compounds of the isatin-blue series.[6] Hydroxyproline with excess of ninhydrin also gives a purple-red colour which can be formulated as due to the hydroxy-derivative of (VI). The purple ninhydrin pigments (VI) differ from the corresponding isatin compounds (III) in that they do not form the characteristic red salts with mineral acids. This



(III)



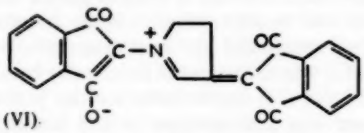
(IV)



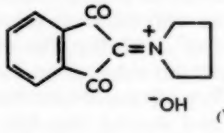
(V)

property is associated with the oxindolylidene cyclic nitrogen atoms which are modified sufficiently in the resonant chromophore as to acquire basic character. It was shown [6] that the pyrolysis of isatin blue gave oxindole; a similar degradation of compound (VI) has given indane-1 : 3-dione, thus confirming that it is the 2-keto-group of ninhydrin which is involved in the condensation with proline.

Pipecolic acid and its derivatives are characterised by purple rather than yellow spots in paper chromatographic analysis by the ninhydrin method.[8] The yellow intermediate corresponding to (IV) is unstable, although it can often be observed as a transient colour, and the product obtained is the purple-red compound corresponding to (VI). This



(VI)



(VII)

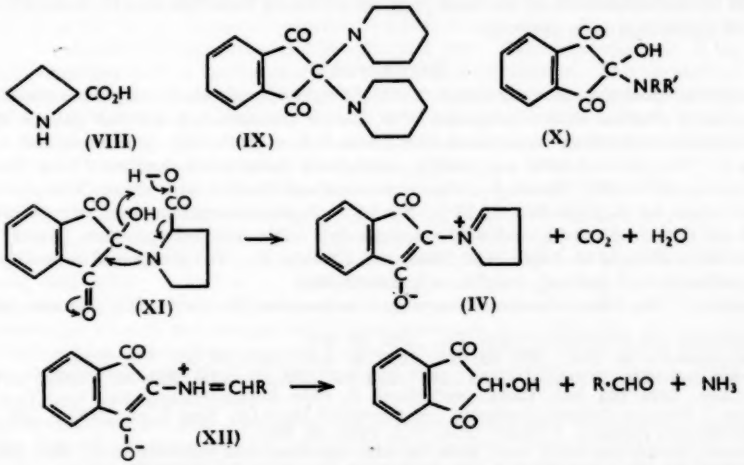
striking difference in the behaviour of the five- and six-membered cyclic α-imino-acids is obviously governed by steric factors and possibly depends upon the equilibrium between (IV) and (VII), enol betaines being known [7] to combine readily with water and alcohols. It has been postulated [9] that, whereas an *exo*-double bond stabilises a five-membered ring, the reverse obtains for six-membered rings. On this basis, the proportion of (VII) in

[6] Johnson and McCaldin, *J.*, 1957, **3470**.
[7] Stafford, *J.*, 1952, 580.
[8] Grobbelaar, Pollard, and Steward, *Nature*, 1955, **175**, 703; Witkop and Foltz, *J. Amer. Chem. Soc.*, 1957, **79**, 192.
[9] Brown, Brewster, and Shechter, *ibid.*, 1954, **76**, 467.

the product would be greater in the proline condensate than in the pipecolic acid product, and hence the activation of the β-position of the ring, a prerequisite for further condensation to the purple compounds of type (VI), is more pronounced with the six-membered cyclic α-imino-acids.

In the same connection, it is of interest to consider the behaviour of azetidine-2-carboxylic acid [10] (VIII) with ninhydrin. This α-imino-acid normally gives a brown colour on paper after treatment with ninhydrin, but if the condensation product [presumably the analogue of (IV)] is treated with excess of ninhydrin and warmed, the colour of the spot changes to blue. The main absorption of the new product in the visible region is at 575 mμ which differs from that for (VI) and corresponds to the colour obtained from a primary amino-acid with ninhydrin.[3] Azetidine-2-carboxylic acid is known [10] to undergo ring fission to homoserine under comparatively mild conditions and it is probable therefore that the blue condensation product is the same as that derived from ninhydrin and homoserine. The effect of ring size on the reaction of the cyclic α-imino-acids with ninhydrin thus causes the formation of a different type of stable condensation product from each of the four-, five-, and six-membered cyclic acids.

As in the condensations with isatin, the corresponding free base may be substituted for the α-imino-acid in the formation of the coloured products of type (VI), if the condensation with ninhydrin is carried out in the presence of hot acetic acid. Pyrrolidine, piperidine, 2-methylpiperidine, and morpholine have been treated with ninhydrin in this manner, and it should be noted that the formation of a coloured compound from 2-methylpiperidine and ninhydrin would not be possible on the Grassmann and Arnim formulation (II) of these compounds. Intermediate compounds were isolated in the reactions of both piperidine and morpholine with ninhydrin. The former has been formulated as (IX) and the latter, a colourless compound, as (X; $RR' = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$). Whereas the proline adduct (IV) crystallised from hot acetic anhydride, the compound (IX) was immediately converted in this solvent into the purple-red condensation product of type (VI); this provides another example of the difference in reactivity between five- and six-membered rings. Proline, piperidine, and morpholine thus yield the three different intermediates (IV), (IX), and (X) which are theoretically possible on the way to the purple pigments.

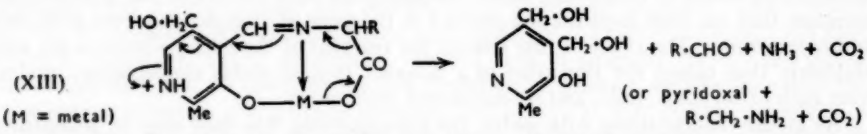



The ease of reaction of ninhydrin with the α-imino-acids (phosphate buffer at pH 7 and 60°), with concomitant loss of carbon dioxide, contrasts with the conditions required for condensation of the corresponding free bases and suggests that the carboxyl group is

[10] Fowden, *Biochem. J.*, 1956, **64**, 323.

involved in the process. It is suggested that the amines or α-imino-acids first form the adducts (X) by a reversible process; but, in the case of the α-imino-acid adducts (XI), operation of the electronic shifts shown, which involves afavourable transition state, results in ready elimination of water and carbon dioxide.

Such a mechanism could apply also to the oxidative decarboxylation [11] of α-amino-acids, $NH_2 \cdot CHR \cdot CO_2H$, to aldehydes, R·CHO, a reaction which can be brought about by ninhydrin, isatins,[12] and a variety of other carbonyl compounds containing electron-withdrawing groups adjacent to the carbonyl group. The reaction is also facilitated by an increase in the electron-attracting powers of the substituent R.[13] The adduct from ninhydrin and the α-amino-acid is visualised as undergoing a concerted electronic change similar to that shown in (XI) to give a Schiff's base (XII) which is




hydrolysed to the aldehyde, R·CHO, ammonia, and 2-hydroxyindane-1 : 3-dione, as observed. This hydrolysis is more difficult in the case of the product from proline where the quaternary nitrogen atom is fully substituted and prototropic rearrangement cannot occur. Somewhat related mechanisms have been discussed by Hine,[14] by Sweeley and Horning,[15] and also in the particular case of the transaminations and decarboxylations of α-amino-acids catalysed by vitamin $B_6$ in the presence of metal ions.[16] The intermediate (XIII) involved in these reactions is clearly related to (XI), and the analogy is strengthened by the observation [17] that substitution on the primary amino-group of the amino-acid, as in proline, prevents the decarboxylation–transamination reaction with pyridoxal. Alternative mechanisms, not involving decarboxylation as an intrinsic step, for the oxidation–decarboxylation of α-amino-acids have been advanced by Schönberg, Moubasher, and their collaborators [18] and by Baddar *et al.*,[19] and it has also been suggested [20] that the effective reagent might be $OH^+$ in certain cases.

Work on the structures of the blue pigments derived from the acyclic *N*-methylamino-acids and ninhydrin is in progress.

## Experimental

Absorption spectra were determined in 95% EtOH except where otherwise stated.

*Reaction of Proline with Ninhydrin. The Yellow Condensation Product* (IV).—This was prepared by the method of Grassmann and Arnim [2] from ninhydrin (900 mg.) and L-proline (540 mg.). The product (875 mg., 82%) crystallised from warm methanol and the yellow crystals, m. p. 190—195° (decomp.), were separated and washed with ether (Found: C, 72·8; H, 5·45. Calc. for $C_{13}H_{11}O_2N$: C, 73·2; H, 5·2). Light absorption max. were at **231**, **303**, and **354** mμ (log ε **4·35**, **4·04**, and **4·26** respectively). The infrared spectrum (Nujol) showed bands at **1661**, **1622**, **1579**, **1446**, **1410**, **1365**, and **1360** cm.$^{-1}$. The compound is readily soluble in polar solvents and sparingly soluble in hydrocarbons.

*Oxidation of the Yellow Proline–Ninhydrin Condensation Product.*—The pigment (400 mg.)

[11] Schönberg and Moubasher, *Chem. Rev.*, 1952, **50**, 261.
[12] Langenbeck *et al.*, *Ber.*, 1927, **60**, 930; 1928, **61**, 942; 1937, **70**, 367, 672, 1039.
[13] Bergel and Bolz, *Z. physiol. Chem.*, 1933, **215**, 25; **220**, 20; 1934, **223**, 66; Herbst and Clarke, *J. Biol. Chem.*, 1934, **104**, 769; Baddar and Sherif, *J.*, 1956, 4292.
[14] Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, 1956, p. 288.
[15] Sweeley and Horning, *J. Amer. Chem. Soc.*, 1957, **79**, 2622.
[16] Metzler, Ikawa, and Snell, *ibid.*, 1954, **76**, 648; Rothberg and Steinberg, *ibid.*, 1957, **79**, 3274.
[17] Herbst, *Adv. Enzymol.*, 1944, **4**, 75; Snell, *J. Amer. Chem. Soc.*, 1945, **67**, 194.
[18] Moubasher *et al.*, *J.*, 1948, 176; 1949, 1137; 1951, 231, 1928; *J. Amer. Chem. Soc.*, 1950, **72**, 2666.
[19] Baddar *et al.*, *J.*, 1949, S 163; 1950, 136; 1954, 209; 1956, 4292; see also Hammick, Roe, Weston, and Whiting, *J.*, 1953, 3825.
[20] Spenser, Crawhall, and Smyth, *Chem. and Ind.*, 1956, 796.

was suspended in an alkaline solution of hydrogen peroxide (0·4 c.c. of 100-vol. hydrogen peroxide in 8 c.c. of 0·5N-aqueous sodium hydroxide) and shaken until all the solid had dissolved. The solution was then acidified with the minimum quantity of concentrated hydrochloric acid and kept overnight; then the white crystalline material (168 mg.) was separated, washed, and dried. It crystallised from benzene–methanol as small prisms, m. p. 185—186° (sealed tube), and was shown to be identical with phthalic acid by colour reactions and conversion into the anhydride.

*Reaction of Hydroxyproline with Ninhydrin.*—Ninhydrin (400 mg.) was dissolved in warm alcohol (5 c.c.), cooled, and added to an aqueous solution (3 c.c.) of L-4-hydroxyproline (250 mg.). The solution became red and carbon dioxide was evolved. The product was concentrated (to *ca.* 3 c.c.) until crystals separated and, after cooling, the solid *product* was removed and washed with a little ethanol, being obtained as dark-brown needles (290 mg.), which after crystallisation from methanol had m. p. 132—133° (decomp.) (Found: C, 67·6; H, 5·0; N, 6·35. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·84; N, 6·1%), $\lambda_{max.}$ 233, 303, and 354 mμ (log ε 4·35, 4·00, and 4·26 respectively).

*Reaction of Proline with Ninhydrin. The Purple Condensation Product* (VI).—(i) Ninhydrin (178 mg.) and L-proline (50 mg.) were dissolved in separate portions of phosphate buffer (pH 7; 2·5 c.c. each), mixed, and heated at 60° on a water-bath for 10 min. The purple-brown precipitate was separated (120 mg.), washed with hot water, and dried; it had m. p. 174—176° (decomp.). Purification was effected by chromatography of a chloroform solution of the product on a column (35 × 2 cm.) of deactivated alumina, most of the impurities being retained on the column. Concentration of the eluate under reduced pressure gave a solution from which the product crystallised as purple needles with a metallic sheen, m. p. 176° (decomp.) (Found: N, 4·1. Calc. for $C_{22}H_{13}O_4N$: N, 3·94%), $\lambda_{max.}$ (in $CHCl_3$) 250, 269, 285, 320, 340, and 545 mμ (log ε 4·42, 4·16, 4·03, 3·56, 3·59, and 4·96 respectively).

(ii) The yellow condensation product (IV) (200 mg.) from proline and ninhydrin was condensed with excess of ninhydrin (530 mg.) according to the method of Grassmann and Arnim.[2] The product (280 mg.) crystallised from chloroform–light petroleum (b. p. 60—80°; 1 : 2). Its ultraviolet and visible absorption spectrum was identical with that of the product of the previous experiment.

(iii) Pyrrolidine (125 mg.) was added to a solution of ninhydrin (500 mg.) in warm 2N-acetic acid (10 c.c.), and the mixture heated to boiling. After cooling, the solid product (280 mg.) was separated and crystallised as before from chloroform–light petroleum (b. p. 60—80°; 1 : 2). The product was identified by means of the visible and ultraviolet absorption spectrum.

*Pyrolysis of the Purple Proline–Ninhydrin Condensation Product.*—The pigment (200 mg.) was heated in a sublimation apparatus at 210—220°/0·1 mm. White crystals (*ca.* 3 mg.), m. p. 127—128°, together with a brown oil, were obtained as sublimate. The crystalline product was separated and gave a negative fluorescein reaction but a strong yellow colour with dilute aqueous sodium hydroxide. The m. p. was not depressed on admixture with authentic indane-1 : 3-dione, m. p. 129—131°. A similar yield of the same product was obtained from the pyrolysis of the purple morpholine–ninhydrin pigment (see below).

*Reaction of Pipecolic Acid with Ninhydrin.*—A solution of ninhydrin (170 mg.) in phosphate buffer (pH 7; 2 c.c.) was mixed with a solution of L-pipecolic acid (85 mg.) in phosphate buffer (pH 7; 2 c.c.), and the reaction which commenced immediately was completed by warming at 60° on the water-bath for 10 min. The solid product (95 mg.) was separated, washed with hot water, and dried; it had m. p. 170° (decomp.) and was purified by adsorption of the impurities from a chloroform solution on a column of deactivated alumina. Concentration of the eluate (to 15 c.c.) and dilution with light petroleum (b. p. 60—80°; 30 c.c.) caused the product (40 mg.) to crystallise as purple needles with a metallic sheen, m. p. 238° (decomp.) (Found: N, 3·4. Calc. for $C_{23}H_{15}O_4N$: N, 3·8%), $\lambda_{max.}$ (in $CHCl_3$) 260, 350, and 571 mμ (log ε 4·42, 3·67, and 4·87 respectively).

*Reaction of Piperidine with Ninhydrin.*—(i) Piperidine (150 mg.) was added to a solution of ninhydrin (500 mg.) in warm 2N-acetic acid (10 c.c.), and the mixture heated to the b. p. After cooling, the solid product (330 mg.) was separated and crystallised from chloroform–light petroleum (b. p. 60—80°; 1 : 2) as purple needles, identical (spectra) with the product from the previous experiment.

(ii) 2 : 2-*Dipiperidinoindane*-1 : 3-*dione.*—Piperidine (190 mg.) was added to a solution of ninhydrin (178 mg.) in ethanol (2 c.c.). The mixture was heated on the water-bath for 20 min.

XUM

and, after cooling, the colourless crystals (190 mg.) were separated and washed with cold ethanol (Found: N, 8·6. Calc. for $C_{19}H_{24}O_2N_2$: N, 8·95%). Light absorption max. were at 228, 281, and 375 mμ (log ε 4·64, 3·31, and 2·59 respectively). The crystals were transformed into a coloured product at >100°.

*Reaction of Morpholine with Ninhydrin.*—(i) A solution of ninhydrin (500 mg.) and morpholine (500 mg.) in aqueous 10% acetic acid (10 c.c.) was boiled for 10 min., then concentrated to *ca.* 1 c.c. under reduced pressure. The precipitated purple product was separated, washed, dried (264 mg.), and purified, first by adsorption of the impurities from a solution in chloroform on deactivated alumina, and secondly by slow crystallisation from hot chloroform (extraction with hot solvent from a thimble) to yield the *product* as dark purple prisms, m. p. 258—260° (decomp.) (Found: C, 70·6; H, 3·75; N, 3·7. $C_{22}H_{13}O_5N$ requires C, 71·15; H, 3·55; N, 3·8%), $\lambda_{max.}$ (in $CHCl_3$) 250, 270, 345, and 554 mμ (log ε 4·43, 4·29, 3·67, and 4·80 respectively).

(ii) *2-Hydroxy-2-morpholinoindane-1 : 3-dione.*—Morpholine (500 mg.) was added to a solution of ninhydrin (500 mg.) in ethanol (5 c.c.). The mixture was warmed on the water-bath for 10 min., then cooled slowly. White crystals were obtained. These recrystallised from ether–light petroleum (b. p. 60—80°; 1 : 2) as needles (420 mg.) (Found: C, 63·1; H, 5·55; N, 5·65. $C_{13}H_{13}O_4N$ requires C, 63·15; H, 5·3; N, 5·65%), $\lambda_{max.}$ 228, 247, 279, and 351 mμ (log ε 4·42, 3·82, 3·00, and 2·15 respectively).

*Reaction of 2-Methylpiperidine with Ninhydrin.*—A solution of ninhydrin (500 mg.) and 2-methylpiperidine (500 mg.) in glacial acetic acid (15 c.c.) was heated on the steam-bath for 10 min. On addition of a few drops of water, the purple condensation *product* (128 mg.) was precipitated. It was separated, washed, dried, and crystallised from chloroform–carbon tetrachloride (1 : 8) as dark purple prisms, m. p. 195—197° (decomp.) (Found: C, 75·0; H, 4·4; N, 3·8. $C_{24}H_{17}O_4N$ requires C, 75·2; H, 4·45; N, 3·65%), $\lambda_{max.}$ (in $CHCl_3$) 248, 345, and 571 mμ (log ε 4·39, 3·69, and 4·11 respectively).

We are grateful to the Directors of the Metal Box Co., Ltd., for granting leave of absence to one of us (D. J. McC) in order to carry out this work. We also thank Dr. T. J. King for a sample of L-pipecolic acid and Dr. L. Fowden for one of azetidine-2-carboxylic acid.

THE UNIVERSITY, NOTTINGHAM. [*Received, August 19th*, 1957.]

---

## 159. *Cyclodehydration Processes. Part I. Benzofuran Derivatives formed by Cyclisation of ω-Aryloxyacetophenones.*

By W. DAVIES and S. MIDDLETON.

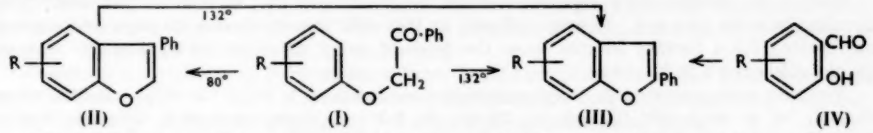
ω-Phenoxyacetophenone and the three isomeric ω-tolyloxyacetophenones are cyclised by polyphosphoric acid at 132° to 2-phenyl- and 7-, 6-, and 5-methyl-2-phenyl-benzofuran respectively; the expected 3-phenylbenzofuran derivatives are not thus obtained. Cyclisation at ≯80° converts ω-phenoxyacetophenone into 3-phenylbenzofuran, which is isomerised to 2-phenylbenzofuran by polyphosphoric acid at 132°.

SINCE cyclodehydration of several phenacyl phenyl sulphides afforded 2- and not 3-substituted thionaphthens,[1] we have investigated the cyclodehydration of several ω-aryloxyacetophenones[2] (I). The literature records many instances[3] in which 3-methylbenzofurans have been prepared by cyclisation of β-ketoalkoxybenzenes, but for the analogous arylbenzofurans the only record is that ω-phenoxyacetophenone is not cyclised by zinc chloride, phosphoric oxide, oxalic acid, sulphuric acid, or sodium.[4]

In the preparation of phenacyl phenyl sulphides by interaction of thiols and aracyl halides, pyridine was found[1] to be an effective condensing medium, but the corresponding reaction with phenols failed owing to the rapid formation of aracyl pyridinium halides. ω-Aryloxyacetophenones (I) are however conveniently made by this reaction in boiling acetone in the presence of potassium carbonate, which is a better method than use of

[1] Banfield, Davies, Gamble, and Middleton, *J.*, 1956, 4791.
[2] For a preliminary note see Davies and Middleton, *Chem. and Ind.*, 1957, 599.
[3] Bradsher, *Chem. Rev.*, 1946, **38**, 455.
[4] Stoermer and Atenstädt, *Ber.*, 1902, **35**, 3560.

aqueous sodium hydroxide. In both methods aracyl chlorides give lower yields than bromides.




Polyphosphoric acid has been found to be an effective cyclising agent for ω-phenoxyacetophenone (I; R = H) and the three ω-tolyloxyacetophenones (I; R = Me), but in each case, ring closure at 132° was accompanied by a rearrangement. The parent compound (I; R = H) gave a 71% yield of 2-phenylbenzofuran identical with a specimen synthesised [5] in a basic medium from salicylaldehyde and ethyl α-bromo-α-phenylacetate. ω-*o*-Tolyloxyacetophenone (I; R = *o*-Me) at 132° afforded only 7-methyl-2-phenylbenzofuran (III; R = 7-Me), identical with a specimen synthesised from 2-hydroxy-3-methylbenzaldehyde (IV; R = 3-Me), and ω-*p*-tolyloxyacetophenone (I; R = *p*-Me) gave 5-methyl-2-phenylbenzofuran (III; R = 5-Me) identical with the product obtained from 2-hydroxy-5-methylbenzaldehyde (IV; R = 5-Me). ω-*m*-Tolyloxyacetophenone (I; R = *m*-Me) gave only 6-methyl-2-phenylbenzofuran (III; R = 6-Me), obtained also from 2-hydroxy-4-methylbenzaldehyde (IV; R = 4-Me).

It is possible that the 3-phenyl isomers are the first cyclisation products, since ω-phenoxyacetophenone in polyphosphoric at room temperature or at 80° affords 3-phenylbenzofuran (II; R = H) identical with a specimen synthesised [6] from 2 : 3-dihydro-3-oxobenzofuran and phenylmagnesium bromide. Moreover, 3-phenylbenzofuran (II; R = H) is isomerised to the 2-phenyl isomer by polyphosphoric acid at 132°. At 110° a mixture of the 2- and 3-phenyl isomers is formed, which recalls the simultaneous appearance [7] of both the isomers when the lactone of *o*-hydroxydiphenylacetic acid was heated with phosphorus tribromide at 200—220°.

The anomalous cyclisation of ω-aryloxyacetophenones is thus in line with that of aracyl phenyl sulphides. For a nitrogen analogue, *N*-phenacylaniline, it has been shown [8] that cyclisation in the presence of an acid catalyst yields 2-phenylindole and that zinc chloride at 170 ° quantitatively converts 3- into 2-phenylindole in 15 minutes.[9] But the 3-phenylindole is not necessarily an intermediate in the formation of the 2-phenyl isomer.[8a]

2-Phenylbenzofurans usually have higher melting points than the corresponding 3-phenyl compounds, as in the thionaphthen series.[1] 2-Phenyl-benzofuran and -naphthalene give a satisfactory trinitrofluorenone derivative but 3-phenylbenzofuran and 1-phenylnaphthalene do not; this has been used to separate mixtures of the 2- and 3-phenylbenzofuran (see p. 824). Aryl-benzofurans and -naphthalenes are also similar in their inability to form stable picrates.

## Experimental

*Preparation of ω-Aryloxyacetophenones.*—Two methods are exemplified in the preparation of ω-phenoxyacetophenone.

*Method* 1. Phenol (9·4 g., 0·1 mol.), phenacyl bromide (19·9 g., 0·1 mol.), and anhydrous potassium carbonate (13·8 g.) were refluxed in acetone (50 ml.) with continuous stirring for 4 hr., then poured into water (500 ml.) and chilled, and the resultant solid crystallised from ethanol, to give ω-phenoxyacetophenone, m. p. 71—72° (15·0 g., 71%). Further recrystallisation from ethanol gave m. p. 72·5—73° [Mohlau [10] reports m. p. 72°, Guss,[11] m. p. 71—72°, and Yates,[12] m. p. 73—73·5° (corr.)]. The 2 : 4-dinitrophenylhydrazone formed orange plates

[5] Kawai, Nakamura, and Sugiyama, *Ber.*, 1939, **72**, 1146.
[6] Stoermer and Barthelmes, *Ber.*, 1915, **48**, 68.
[7] Stoermer, *Ber.*, 1903, **36**, 3990.
[8] Mann and his co-workers, *J.*, (*a*) 1943, 58; (*b*) 1948, 847, 858, and references cited therein.
[9] Fischer and Schmidt, *Ber.*, 1888, **21**, 1811.
[10] Mohlau, *Ber.*, 1882, **15**, 2498.
[11] Guss, *J. Amer. Chem. Soc.*, 1949, **71**, 3462.
[12] Yates, *ibid.*, 1952, **74**, 5380.

(from ethanol–benzene), m. p. 182·5—183·5° [Guss [11] reports m. p. 183—184° (uncorr.)]. When the bromide was replaced by the chloride (15·5 g., 0·1 mol.), a 30% yield was obtained.

*Method* 2. Adding 10% aqueous sodium hydroxide (50 ml.) to phenol (0·1 mol.) and phenacyl bromide (0·1 mol.) in water (30 ml.) at 100° with stirring during 30 min., and stirring and heating for a further 30 min. gave the product, m. p. 70—72° (12·4 g., 58%). Use of the chloride gave a 25% yield.

Similarly were prepared ω-o-*tolyloxyacetophenone* (method 1, 57%; 2, 36%), needles (from ethanol), m. p. 62·5—63° (Found: C, 79·45; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%) [2 : 4-*dinitrophenylhydrazone*, orange needles (from ethanol–benzene), m. p. 186·5—187·5° (Found: N, 13·4. $C_{21}H_{18}N_4O_5$ requires N, 13·8%)], ω-*m*-tolyloxyacetophenone (method 1, 51%; 2, 42%), needles (from ethanol), m. p. 74—74·5° (Found: C, 79·9; H, 6·3%) (Kunckell [13] reports m. p. 84°) [2 : 4-*dinitrophenylhydrazone*, prisms (from ethanol–benzene), m. p. 183·5—184·5° (Found: N, 13·45%)], and ω-*p*-tolyloxyacetophenone (method 1, 54%; 2, 38%), needles (from ethanol), m. p. 64·5—65·5° (Found: C, 79·5; H, 6·4%) (Kunckell [13] reports m. p. 68°) [2 : 4-*dinitrophenylhydrazone*, needles (from ethanol–benzene), soften at 181—183° and change into prisms, m. p. 186—186·5° (Found: N, 13·7%)].

Phenol (9·4 g., 0·1 mol.) and phenacyl chloride (15·5 g., 0·1 mol.) were heated in pyridine (25 ml.) at 100°. After 40 min. crystals began to appear and after a further 20 min. the mixture had completely solidified. Filtration and recrystallisation (charcoal) from 95% ethanol gave needles (very soluble in cold water), m. p. 108—109°; Babcock *et al.*[14] report m. p. 109—110° for phenacylpyridinium chloride monohydrate. The same product was obtained in 2 hr. at room temperature. Use of phenacyl bromide gave phenacylpyridinium bromide, prisms (from ethanol), m. p. 198—199° (decomp.); Baker [15] reports m. p. 199—200° (decomp.).

*Cyclisation of ω-Aryloxyacetophenones.*—The polyphosphoric acid was prepared from phosphoric oxide (420 g.) and phosphoric acid (200 ml.; *d* 1·75).

The cyclisation procedure was as follows: Polyphosphoric acid (20 g.) was preheated at the desired temperature for 20 min. and then 2·0 g. of the compound were added all at once. After being heated with continuous stirring for the desired time, the reactants were cooled, treated with water (500 ml.), and steam-distilled.

(i) ω-*Phenoxyacetophenone*. At 132° (chlorobenzene bath) for 2 hr. this compound gave 2-phenylbenzofuran which recrystallised (charcoal) from ethanol in plates (71%), m. p. and mixed m. p. 121° (Found: C, 86·7; H, 5·3. Calc. for $C_{14}H_{10}O$: C, 86·6; H, 5·2%); von Kostanecki and Tambor,[16] and Stoermer and Reuter,[17] report m. p. 120—121°. It yielded a 2 : 4 : 7-*trinitrofluorenone derivative*, orange-red needles (from absolute ethanol–benzene), m. p. and mixed m. p. 169—170° (Found: N, 8·2. $C_{13}H_5N_3O_7$,$C_{14}H_{10}O$ requires N, 8·25%). Cyclisation at 179° for 2—4 hr. gave 56—45% yields.

Cyclisation at 80° for 3½ hr. gave 3-phenylbenzofuran (1·5 g., 82%), b. p. 110°/0·3 mm., m. p. 42—43°, mixed m. p. 41—42°. Lower yields were obtained by reaction at 80° for 1 hr. or at room temperature for 7 hr.

Reaction at 110° (2 hr.) gave a mixture of 2- and 3-phenylbenzofuran. A distilled specimen was treated in 1 : 1-benzene–absolute alcohol with an excess of 2 : 4 : 7-trinitrofluorenone in the same solvent. The precipitated complex (mixed m. p.) of 2-phenylbenzofuran was collected. The mother-liquor was passed through an alumina column, followed by benzene. Concentration of the colourless eluate gave 3-phenylbenzofuran, m. p. 42—43° and mixed m. p. 40—42°.

(ii) ω-*Tolyloxyacetophenones*. Only the cyclisations at 132° during 2 hr. are now reported. The products were:

6-Methyl-2-phenylbenzofuran (50%), needles (from ethanol); m. p. and mixed m. p. 140—140·5° (Found: C, 86·65; H, 6·0. Calc. for $C_{15}H_{12}O$: C, 86·5; H, 5·8%) (Stoermer [18] reports m. p. 135·5° [2 : 4 : 7-*trinitrofluorenone compound*, orange needles (from absolute ethanol–benzene), m. p. 153—154° (Found: N, 7·8. $C_{13}H_5N_3O_7$,$C_{15}H_{12}O$ requires N, 8·0%)].

5-Methyl-2-phenylbenzofuran (61%), needles (from ethanol), m. p. and mixed m. p. 130—130·5° (Found: C, 86·7; H, 5·8%) (Stoermer [18] reports m. p. 129°) [2 : 4 : 7-*trinitrofluorenone compound*, orange needles (from absolute ethanol–benzene), m. p. 145° (Found: N, 7·9%)].

[13] Kunckell, *Ber.*, 1897, **30**, 577.
[14] Babcock, Nakamura, and Fuson, *J. Amer. Chem. Soc.*, 1932, **54**, 4408.
[15] Baker, *J.*, 1932, 1155.
[16] von Kostanecki and Tambor, *Ber.*, 1909, **42**, 826.
[17] Stoermer and Reuter, *Ber.*, 1903, **36**, 3981.
[18] Stoermer, *Ber.*, 1911, **44**, 1853.

7-*Methyl*-2-*phenylbenzofuran* (55%), an oil which, purified through the 2 : 4 : 7-*trinitrofluorenone compound*, m. p. 191—192° (Found: N, 7·95%), afforded prisms (from ethanol), m. p. 32·5—33° (Found: C, 86·7; H, 6·0%). The mother-liquors from the trinitrofluorenone compound preparation were passed through an alumina column, followed by benzene: no product was present in the eluate [cf. (i) above.]

*Independent Syntheses of* 2-*Phenylbenzofurans*.—2-Phenylbenzofuran was prepared by the method of Kawai *et al.*[5] from ethyl α-bromo-α-phenylacetate and salicylaldehyde. Similarly were obtained 5- (21%), 6- (28%), and 7-methyl-2-phenylbenzofuran (48%).

3-*Phenylbenzofuran*.—(a) *Synthesis*. 2 : 3-Dihydro-3-oxobenzofuran (from *o*-hydroxy-ω-chloroacetophenone by the method of Fries and Pfaffendorf [19]) (8·2 g., 1 mol.) in dry benzene (100 ml.) was added during 20 min. to phenylmagnesium bromide [from bromobenzene (28·8 g., 3 mol.) and magnesium (4·4 g., 3 mol.)] in dry ether (100 ml.). After 2 hr. on a steam-bath, the mixture was decomposed with ice and hydrochloric acid, and the ether layer washed with 2N-sodium hydroxide until the washings were almost colourless. The dried ($CaCl_2$) ether solution was then concentrated, to give 3-phenylbenzofuran (3·7 g., 31%), b. p. 110°/0·3 mm., m. p. 42—43° (Found: C, 86·8; H, 5·4%), which did not give a picrate or 2 : 4 : 7-trinitrofluorenone compound. Stoermer and Barthelmes [6] obtained only a " small yield " of 3-phenylbenzofuran by this method. Stoermer and Kippe [20] report m. p. 42°.

(b) *Isomerisation*. 3-Phenylbenzofuran (1·0 g.) was heated with polyphosphoric acid (20 g.) at 132° for 2 hr. Steam-distillation then gave 2-phenylbenzofuran, m. p. and mixed m. p. 120—121° (0·8 g., 80%).

The authors thank Monsanto Chemicals (Aust.) for a Research scholarship (to S. M.). The microanalyses were carried out by Dr. W. Zimmermann and his staff.

UNIVERSITY OF MELBOURNE, AUSTRALIA. [*Received, September 3rd*, 1957.]

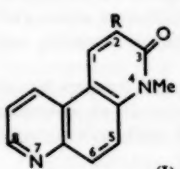
[19] Fries and Pfaffendorf, *Ber.*, 1910, **43**, 214.
[20] Stoermer and Kippe, *ibid.*, 1903, **36**, 4006.

## 160. *The Nitration Product of* 3 : 4-*Dihydro*-4-*methyl*-3-*oxo*-4 : 7-*phenanthroline*.

By W. O. SYKES.

The mononitration product of 3 : 4-dihydro-4-methyl-3-oxo-4 : 7-phenanthroline is shown by various evidence, including unequivocal synthesis of the chloro-analogue, to be the unexpected 2-nitro-compound; hence this phenanthroline undergoes nitration as a cinnamic lactam.

THE base 4 : 7-phenanthroline is not nitrated [1] by treatment with a mixture of fuming nitric acid and concentrated sulphuric acid at 100° but its dihydro-*N*-methyl-oxo-derivative (I; R = H) is converted thereby [2] into a mononitro-compound (*A*). Kaufmann and Radošević [2] reasoned from the 6-nitration [3] (quinoline numbering) of *N*-methylcarbostyril that (*A*) has the nitro-group in a *Bz*-position, probably 5 (phenanthroline numbering); a *Bz*-substitution would accord, also, with the proved 6-nitrations [4] (phenanthroline numbering) of 3-phenyl-4 : 7-phenanthroline and its 1-carboxylic acid derivative. However, it has been shown [5] that the amino-compound obtained by reducing the nitration product (*A*) is neither 5- nor 6-amino-3 : 4-dihydro-4-methyl-3-oxo-4 : 7-phenanthroline, and the work described here indicates which of the five available *Pyr*-positions is occupied by the substituent group.



(I)

[1] Haworth and Sykes, *J.*, 1944, 311.
[2] Kaufmann and Radošević, *Ber.*, 1909, **42**, 2612.
[3] Decker, *J. prakt. Chem.*, 1901, **64**, 85.
[4] Willgerodt and Jablonski, *Ber.*, 1900, **33**, 2918.
[5] Sykes, *J.*, 1953, 3543.

Oxidising the nitro-compound (*A*) with hot aqueous potassium permanganate gave quinolinic acid (in small yield). The same product was similarly obtained from the chloro-analogue (*B*), which was prepared by carrying out a Sandmeyer reaction on the amino-compound derived from (*A*) by reduction with ammonium sulphide.[5] An 8-, 9-, or 10-substituted compound would have been degraded to a substituted quinolinic or nicotinic acid, and the above finding therefore excluded further consideration of the three substituent positions in the unmodified pyridine ring; one of them (8) was also eliminated by the fact that the chloro-compound (*B*) is not identical with the 8-chloro-3 : 4-dihydro-4-methyl-3-oxo-4 : 7-phenanthroline prepared independently.[6] Evidence distinguishing between the remaining possibilities of 1- and 2-substitution was sought from the synthesis of a 2-substituted comparison compound as follows:

6-Nitroquinoline was converted by sulphur dichloride at 100° into its 3-chloro-derivative which was identified by degrading it to 3-chloroquinoline by way of the 6-amino-compound. (3-Chloroquinoline for comparison was prepared from 3-aminoquinoline by a Sandmeyer reaction; it had previously been prepared by chlorination of quinoline.[7]) The methiodide of 6-acetamido-3-chloroquinoline was converted by a Skraup reaction, into another quaternary salt which was isolated as the iodide and on oxidation with ferricyanide gave the compound (*B*), which must therefore have formula (I; R = Cl); and it follows that compound (*A*) is 3 : 4-dihydro-4-methyl-2-nitro-3-oxo-4 : 7-phenanthroline (I; R = $NO_2$).

The 2-nitration of the phenanthroline (I; R = H) by a reagent which provides oxides of nitrogen resembles nitration of certain unsaturated hydrocarbons,[8] which was invoked by Dewar and Maitlis [9] to account for the 3-nitration of quinoline by way of a postulated 1 : 2-adduct. It has a closer parallel in the α-nitration [10,11] of ethyl 3- and 4-nitrocinnamate. Further, 6-nitrocoumarin, a cinnamic lactone analogous to (I; R = H), is nitrated [12] in the corresponding position 3, and *N*-methyl-6-nitrocarbostyril, the equivalent lactam, is nitrated at both position 8 and a *Pyr*-position (unidentified).[13] Thus, cinnamic acid derivatives in which the benzene ring is suitably inactivated are nitrated in the side-chain, commonly, if not invariably, in the α-position; by conforming to this pattern, compound (I; R = H) manifests its character as a " pyridocinnamic lactam."

## Experimental

*Degradation of Kaufmann and Radošević's Nitro-compound.*—The nitro-compound [2] (1 g.) was refluxed with potassium permanganate (7 g.) in water (200 c.c.) until all the permanganate had disappeared (several hours). The precipitated manganese dioxide was filtered off and the filtrate together with hot-water washings was concentrated to small volume and acidified with acetic acid. Copper acetate solution was added, and the blue deposit which was formed very slowly was suspended in hot water and freed from copper with hydrogen sulphide. The crystalline residue (0·1 g.) which remained when the filtrate was evaporated to dryness recrystallised from water as colourless prisms, m. p. about 220° after a transition at about 185°. Quinolinic acid decomposes at about 190°, depending on the rate of heating, to nicotinic acid which has m. p. 232°.

A batch of crude degradation product was heated to its decomposition point (carbon dioxide evolved; lime-water test). The residue crystallised from alcohol (charcoal) as colourless needles, m. p. 231° with previous softening, alone and in admixture with authentic nicotinic acid (m. p. 232°).

[6] Sykes, *J.*, 1956, 3087.
[7] Edinger and Lubberger, *J. prakt. Chem.*, 1896, **54**, 340.
[8] Hückel, " Theoretical Principles of Organic Chemistry," Elsevier, Amsterdam, 1955, Vol. I, pp. 750, 751.
[9] Dewar and Maitlis, *J.*, 1957, 944.
[10] Friedländer and Lazarus, *Annalen*, 1885, **229**, 233.
[11] Friedländer and Mähly, *ibid.*, p. 210.
[12] Clayton, *J.*, 1910, 1388.
[13] Kaufmann and de Petherd, *Ber.*, 1917, **50**, 342.

3-*Chloro*-6-*nitroquinoline*.—6-Nitroquinoline (4 g.) was heated with sulphur dichloride (10 c.c.) in a sealed tube at 100° for 4 hr. The solid product was washed free from sulphur chlorides with ether, then dissolved in hot, dilute hydrochloric acid and precipitated with aqueous ammonia from the filtered solution. The *chloronitroquinoline* crystallised slowly from alcohol (charcoal) as almost colourless prismatic needles (2 g.), m. p. 145° (Found: C, 51·9; H, 2·7; Cl, 16·9. $C_9H_5O_2N_2Cl$ requires C, 51·8; H, 2·4; Cl, 17·0%). Bachmann and Cooper [14] give m. p. 145° (corr.) for a chloro-6-nitroquinoline which they suggest might be the 3-chloro-compound.

6-*Amino*-3-*chloroquinoline*.—3-Chloro-6-nitroquinoline (4 g.) was reduced with aqueous ammonium sulphide as described [6] for reduction of 6-nitroquinoline. The mixture was decomposed with hydrochloric acid, filtered, and made alkaline with aqueous ammonia; the precipitated *aminochloroquinoline* (2·6 g.) crystallised from chlorobenzene as yellow prismatic needles, m. p. 170—171° (Found: C, 60·0; H, 4·0. $C_9H_7N_2Cl$ requires C, 60·5; H, 4·0%).

The *acetyl* derivative, obtained in excellent yield by heating the amine in glacial acetic acid with excess of acetic anhydride for 10 min., crystallised from alcohol as colourless prisms, m. p. 213—214° (Found: C, 59·4; H, 4·3. $C_{11}H_9ON_2Cl$ requires C, 59·9; H, 4·1%).

*Evidence for* 3-*Chlorination of* 6-*Nitroquinoline*.—6-Amino-3-chloroquinoline (1·2 g.) was diazotised and reduced with ethanol as described [15] for the 8-amino-isomer. A yellowish oil was obtained by steam-distilling the basified reaction mixture; it formed a picrate (0·6 g.), yellow needles, m. p. 186—187°, from alcohol. Baker *et al.*[15] give m. p. 187—189°, and Meisenheimer [16] gives m. p. 182° for the picrate of 3-chloroquinoline obtained in both cases by chlorinating quinoline with sulphur dichloride.[7] The structure of this presumed 3-chloro-derivative has not been satisfactorily proved, because the degradation product claimed [7] to be 5-chloronicotinic acid cannot in fact be this acid; [17] the analytical results quoted for the product do not agree with the requirements for a chloroquinolinic acid. On the other hand, although the b. p. (255°/743 mm.) is not sharply differentiated from those of the other mono-chloroquinolines (b. p.s of all seven fall within the range 255—290°), the m. p. of the picrate is well removed at least from those of 2- and 4-chloroquinoline picrate. We were unable to obtain a sample of 3-chloroquinoline of satisfactory purity by Edinger and Lubberger's [7] method on a reduced scale, but prepared the compound by a Sandmeyer reaction from 3-aminoquinoline (crude yield 1 g. from 5 g.). A chief fraction, b. p. 259°/770 mm. (Found: Cl, 21·1. Calc. for $C_9H_6NCl$: Cl, 21·7%), distilled from several combined preparations, formed a picrate, m. p. 186—187° not depressed by admixture with the first-mentioned picrate, above.

6-*Acetamido*-3-*chloro*-1-*methylquinolinium Iodide*.—6-Acetamido-3-chloroquinoline (2 g.) was heated in a sealed tube with an excess of methyl iodide in methanol for 30 min. at 100°; the yellow *methiodide* (3 g.) crystallised from water (charcoal) as needles, m. p. (decomp.) about 250° with previous darkening (Found: I, 35·0. $C_{12}H_{12}ON_2ClI$ requires I, 35·0%).

2-*Chloro*-4-*methyl*-4 : 7-*phenanthrolinium Iodide*.—6-Acetamido-3-chloroquinoline methiodide (4 g.) was subjected to a Skraup reaction in the conditions described [5] for the 8-chloro-isomer, and the *chlorophenanthroline methiodide* (1·6 g.) was isolated by adding potassium iodide solution to the diluted, nearly neutralised reaction mixture. The new methiodide crystallised from water (charcoal) as orange prisms which darkened and softened above 240° and decomposed at about 260° (Found: I, 35·6. $C_{13}H_{10}N_2ClI$ requires I, 35·6%).

2-*Chloro*-3 : 4-*dihydro*-4-*methyl*-3-*oxo*-4 : 7-*phenanthroline*.—(*a*) The preceding methiodide (1·0 g.) was oxidised with potassium ferricyanide in alkaline solution. The *dihydro*-N-*methyl*-*oxo*-*compound* (0·6 g.) was precipitated promptly when the reagents were mixed, and was purified by way of the sulphate which crystallised on cooling of a solution of the base in hot, dilute sulphuric acid (charcoal); it crystallised from chlorobenzene as almost colourless needles, m. p. 240° (Found: C, 63·5; H, 3·8; Cl, 14·8. $C_{13}H_9ON_2Cl$ requires C, 63·8; H, 3·7; Cl, 14·5%).

(*b*) Kaufmann and Radošević's amino-compound [2,5] (4·5 g.) in hot, concentrated hydrochloric acid was cooled in ice, to produce a finely crystalline suspension of the hydrochloride, and sodium nitrite (1·5 g.) in water was added gradually with vigorous shaking between additions. The deep red diazotised solution was added gradually to cuprous chloride (2 g.) in concentrated hydrochloric acid (20 c.c.) at 0° (copious frothing) and the mixture was set aside for ½ hr. A

[14] Bachmann and Cooper, *J. Org. Chem.*, 1944, **9**, 302.
[15] Baker, Albisetti, Dodson, Lappin, and Riegel, *J. Amer. Chem. Soc.*, 1946, **68**, 1532.
[16] Meisenheimer, *Ber.*, 1926, **59**, 1848.
[17] von Pechmann and Mills, *Ber.*, 1904, **37**, 3829.

XUM

hot, aqueous solution (charcoal) of the precipitated hydrochloride was decomposed with aqueous ammonia; the precipitated base (3 g.), crystallised from chlorobenzene, had m. p. 241°, unchanged by admixture with the above dihydro-*N*-methyl-oxo-compound.

My thanks are offered to Mr. J. A. Davidson for assistance in the preparative work.

CHARING CROSS HOSPITAL MEDICAL SCHOOL, DEPARTMENT OF BIOCHEMISTRY,
13 WILLIAM IV STREET, LONDON, W.C.2. [*Received, September 16th*, 1957.]

---

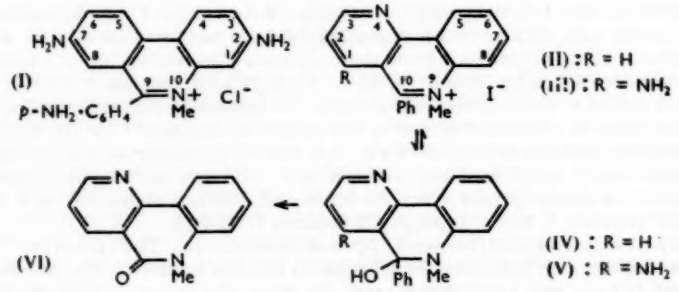
## 161. *A Search for New Trypanocides. Part V.* Some Derivatives of 10-Phenyl-4 : 9-diazaphenanthrene.*

By M. DAVIS.

Several quaternary salts derived from 10-phenyl-4 : 9-diazaphenanthrene, an aza-analogue of 9-phenylphenanthridine, have been prepared as potential trypanocides. Only three compounds showed weak activity against *Trypanosoma congolense* in mice. None was active against *T. rhodesiense*.

4 : 9-DIAZAPHENANTHRENE has features in common with both phenanthridine and 4-aminoquinoline and it was considered possible that suitably constituted derivatives might possess the trypanocidal activity shown by many compounds derived from these systems.[1]

Only a few 4 : 9-diazaphenanthrenes are recorded in the literature. Marckwald [2] applied the Skraup and Döbner–Miller reactions to 4-aminoquinaldine and obtained small amounts of 10-methyl- and 3 : 10-dimethyl-4 : 9-diazaphenanthrene. Lions and Ritchie [3] showed that 4-aminoquinaldine failed to undergo the Conrad–Limpach reaction, but reacted at 160° with acetoacetic ester, the resulting amide being cyclised by concentrated sulphuric acid to 3-hydroxy-1 : 10-dimethyl-4 : 9-diazaphenanthrene. Hauser and Reynolds [4] subjected 4-aminoquinoline to the Conrad–Limpach, Knorr, and ethoxymethylenemalonic ester syntheses, obtaining 1-hydroxy-3-methyl- and 3-hydroxy-1-methyl-4 : 9-diazaphenanthrene and ethyl 1-hydroxy-4 : 9-diazaphenanthrene-2-carboxylate, respectively.




In the phenanthridine series trypanocidal activity, which is perceptible even in 10-methyl-9-phenylphenanthridinium chloride, increases steadily as one, two, or three amino-groups are introduced (in appropriate positions) into the molecule, one of the most active compounds being Trimidium chloride [5] (I). It was decided, therefore, to prepare the analogous 9-methyl-10-phenyl-4 : 9-diazaphenanthrene 9-methiodide (II) and to

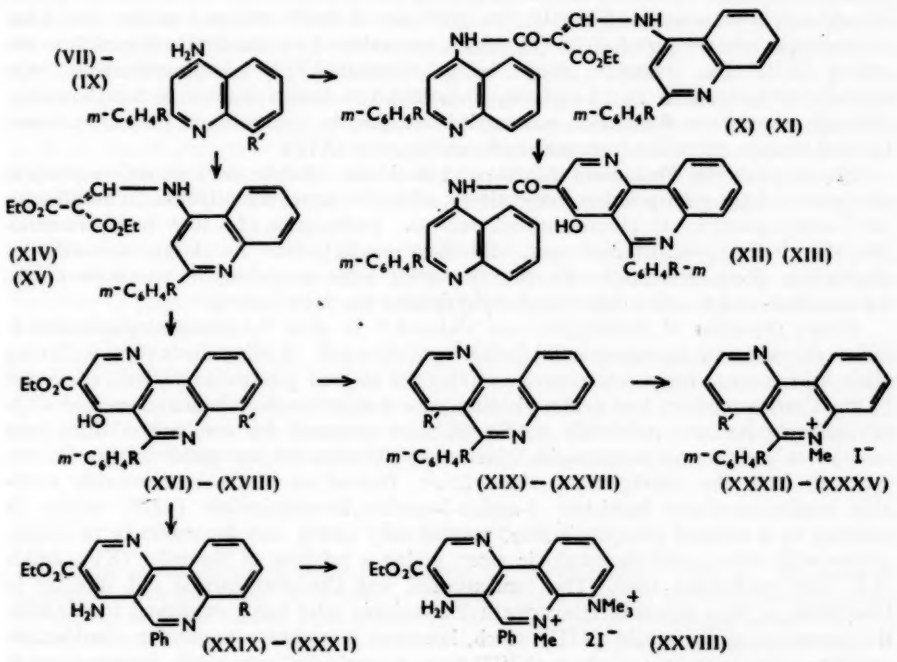
* Part IV, Ashley and Davis, *J.*, 1957, 812.

[1] *E.g.*, Walls, *J.*, 1950, 3511 and earlier papers; Jensch, *Annalen*, 1950, **568**, 73 and earlier papers; Pratt and Archer, *J. Amer. Chem. Soc.*, 1948, **70**, 4065.
[2] Marckwald, *Annalen*, 1894, **279**, 1.
[3] Lions and Ritchie, *J. Proc. Roy. Soc., New South Wales*, 1940, **74**, 443.
[4] Hauser and Reynolds, *J. Org. Chem.*, 1950, **15**, 1224.
[5] Walls and Whittaker, *J.*, 1950, 43.

investigate the effect of introducing amino- and ethoxycarbonylamino-groups into the molecule.

10-Phenyl-4 : 9-diazaphenanthrene was obtained in moderate yield from 4-amino-2-phenylquinoline (VII) by the Skraup reaction and was converted by excess of methyl iodide into a monomethiodide, considered to be (II). It is not the 4-methiodide because its aqueous solution with dilute ammonia afforded the water-insoluble pseudo-base (IV) which was unaffected by boiling alkaline ferricyanide but regenerated the original methiodide on treatment in dilute hydrochloric acid with potassium iodide.[6]

Introduction of an amino-group into the newly formed pyridine ring of the 4 : 9-diazaphenanthrene was next attempted, the 1-position being selected as being, not only the most accessible, but also capable of exhibiting the tautomerism characteristic of 4-aminoquinoline derivatives, some of which are active trypanocides.




| | R | R′ |
|---|---|---|
| VII | H | H |
| VIII | $NO_2$ | H |
| IX | H | $NO_2$ |
| X | H | |
| XI | $NO_2$ | |
| XII | H | |
| XIII | $NO_2$ | |
| XIV | H | |
| XV | $NO_2$ | |
| XVI | H | H |

| | R | R′ |
|---|---|---|
| XVII | $NO_2$ | H |
| XVIII | H | $NO_2$ |
| XIX | H | OH |
| XX | H | Cl |
| XXI | H | $NH_2$ |
| XXII | H | OPh |
| XXIII | $NO_2$ | Cl |
| XXIV | $NO_2$ | OPh |
| XXV | $NH_2$, HCl | H |

| | R | R′ |
|---|---|---|
| XXVI | $NH_2$ | $NH_2$ |
| XXVII | NH·$CO_2$Et | NH·$CO_2$Et |
| XXIX | $NH_2$ | |
| XXX | NHAc | |
| XXXI | NH·$CO_2$Et | |
| XXXII | NHAc | NHAc |
| XXXIII | $NMe_3$I | $NH_2$ |
| XXXIV | $NH_2$ | $NH_2$ |
| XXXV | NH·$CO_2$Et | NH·$CO_2$Et |

4-Amino-2-phenylquinoline failed to condense with acetoacetic ester in boiling ethanol (containing a catalytic amount of hydrochloric acid), but treatment with excess of the ester above 180° afforded 4-acetoacetamido-2-phenylquinoline in low yield. However, it reacted readily with ethoxymethylenemalonic ester in boiling xylene (although not in

[6] Cf. Petrow and Wragg, *J.*, 1947, 1410; 1950, 3516.

chloroform).[7] The expected diethyl (2-phenyl-4-quinolylaminomethylene)malonate (XIV) was accompanied by the monoamide (X), formed by interaction of the diester with a further molecule of the base; this was readily cyclised in boiling Dowtherm to the diazaphenanthrene amide (XII) which was also formed in appreciable amounts when 4-amino-2-phenylquinoline and ethoxymethylenemalonic ester were condensed together directly in boiling Dowtherm. Similar amides have been encountered during the preparation of 4-aminoquinoline from aniline.[8] Diethyl (2-phenyl-4-quinolylaminomethylene)malonate was cyclised in boiling Dowtherm to the diazaphenanthrene (XVI) which was hydrolysed and decarboxylated to 1-hydroxy-10-phenyl-4 : 9-diazaphenanthrene (XIX).

The corresponding 1-chloro-compound (XX), prepared from this phenol by phosphorus oxychloride, reacted with ammonia in boiling phenol,[9] giving the required 1-amino-10-phenyl-4 : 9-diazaphenanthrene (XXI). At a slightly lower temperature amination was incomplete and the 1-phenoxy-derivative (XXII) was also isolated. The amino-compound formed only a monomethiodide (III), the structure of which follows from its conversion by ammonia into the pseudo-base (V), which was oxidised by alkaline ferricyanide to the amide (VI), the phenyl group being eliminated.[6,10] 4-Aminoquinaldine was similarly converted into ethyl 1-hydroxy-10-methyl-4 : 9-diazaphenanthrene-2-carboxylate, although when the condensation was carried out directly in Dowtherm the only product isolated was the diazaphenanthrene amide analogous to (XII).

The trypanocides Phenidium chloride and Metidium chloride carry an amino-group in the *para*- and the *meta*-position, respectively, of the 9-phenyl substituents, in addition to the 7-amino-group in the phenanthridine nucleus. Preparation of a 10-*p*- or 10-*m*-aminophenyl-4 : 9-diazaphenanthrene was therefore undertaken. As large amounts of cinchophen (2-phenylquinoline-4-carboxylic acid) were available, its conversion into 4-amino-2-*m*- and 4-amino-2-*p*-nitrophenylquinoline was investigated.

Direct nitration of cinchophen was claimed[11] to give 2-*p*-nitrophenylquinoline-4-carboxylic acid, but no experimental details were recorded. Adding cinchophen to fuming nitric acid at room temperature gave a mixture of *m*- and *p*-nitro-derivatives, converted by the Curtius reaction into azides yielding pure 4-ethoxycarbonylamino-2-*m*- and -2-*p*-nitrophenylquinoline. Authentic specimens were prepared for comparison from pure samples of the *m*- and *p*-nitro-acid, which were obtained (in low yield) by the Döbner synthesis from the corresponding aldehydes.[11] Hydrolysis of the more readily available *m*-nitro-urethane furnished 4-amino-2-*m*-nitrophenylquinoline (VIII) which, in contrast to 4-amino-2-phenylquinoline, reacted only slowly and incompletely in boiling xylene with ethoxymethylenemalonic ester, giving a mixture of the ester (XV), amide (XI), and unchanged base. The condensation was therefore carried out directly in Dowtherm, a large excess of ethoxymethylenemalonic ester being employed to minimise the formation of the amide (XIII) which, however, was always present in considerable quantity. The principal product (XVII) was successively hydrolysed, decarboxylated, and chlorinated in the usual manner. Amination of 1-chloro-10-*m*-nitrophenyl-4 : 9-diazaphenanthrene (XXIII) in phenol at 190—200° gave only the 1-phenoxy-compound (XXIV) and longer heating at higher temperatures led to extensive decomposition. Preliminary catalytic reduction of the nitro-group was hence carried out, Raney nickel in ethanol being used since concomitant dehalogenation to 10-*m*-aminophenyl-4 : 9-diazaphenanthrene hydrochloride (XXV) was much less than when platinum oxide or palladium oxide was employed. 10-*m*-Aminophenyl-1-chloro-4 : 9-diazaphenanthrene, thus prepared, reacted normally with ammonia in phenol, giving the 1-amino-compound (XXVI) in almost quantitative yield. The diacetyl derivative of this base gave a monomethiodide,

[7] Cf. Steck, Hallock, and Suter, *J. Amer. Chem. Soc.*, 1948, **70**, 4063.
[8] Kermack and Storey, *J.*, 1950, 607.
[9] Backeberg and Marais, *J.*, 1942, 381; Albert, Brown, and Duewell, *J.*, 1948, 1284.
[10] Schofield and Theobald, *J.*, 1951, 2992.
[11] D.R.-P. 279,195.

XUM

considered to be (XXXII), which was hydrolysed to the required 1-amino-10-*m*-aminophenyl-4 : 9-diazaphenanthrene 9-methiodide (XXXIV).

The diamine (XXVI) with methyl iodide and sodium carbonate in methanol afforded a bismethiodide which is probably (XXXIII). The diamine gave the expected bisurethane (XXVII), which was likewise converted into its 9-methiodide (XXXV).

The highly active trypanocide Dimidium bromide contains amino-groups in the 2 : 7-positions of the phenanthridine system, the 9-phenyl group remaining unsubstituted. The preparation of a nuclear diamino-10-phenyldiazaphenanthrene was therefore investigated, although initially no attempt was made to obtain an exact positional analogue. 8-Nitro-2-phenylquinoline-4-carboxylic acid,[12] which is readily available, was converted by the Curtius reaction into 4-amino-8-nitro-2-phenylquinoline (IX). This with a large excess of ethoxymethylenemalonic ester in Dowtherm gave the diazaphenanthrene (XVIII) in good yield, no appreciable quantity of amide by-product being produced. The corresponding acid could not be satisfactorily decarboxylated in Dowtherm, either as the free acid or as the silver salt. Difficulties in the decarboxylation of 3-carboxy-4-hydroxyquinolines containing nitro-groups in the benzene ring have been previously encountered.[13] The remaining stages of the synthesis were therefore carried out on the ester (XVIII). This was successively chlorinated, aminated in phenol, and reduced catalytically to ethyl 1 : 8-diamino-10-phenyl-4 : 9-diazaphenanthrene-2-carboxylate (XXIX). The latter diamine formed a monoacetyl derivative and a monourethane, probably the 8-derivatives (XXX) and (XXXI) respectively. Neither derivative could be quaternised, probably for steric reasons.[14]

The original diamine (XXIX) gave a bismethiodide, probably (XXVIII).

In view of the low trypanocidal activity found with these compounds the original intention of preparing derivatives more closely related to the active phenanthridines was not further pursued.

The author thanks Mrs. R. Stone, B.Sc., for the following biological results: the methiodides (XXXIV), (XXXV), and (XXXVIII) were effective, but not curative against *T. congolense* in mice; they were inactive against *T. rhodesiense*. Compounds (II), (III), and (XXXIII), the hydrochlorides of (XIX), (XXI), (XXVI), (XXIX), and (XXXI), and the metho(methyl sulphate) of (XX) were inactive against both organisms.

## Experimental

*4-Acetoacetamido-2-phenylquinoline.*—4-Amino-2-phenylquinoline [15] (0·5 g.) in excess of acetoacetic ester was boiled for 1 min., and the solution was cooled and evaporated *in vacuo*. Crystallisation of the residue from ethanol gave *4-acetoacetamido-2-phenylquinoline* (0·2 g.) in needles, m. p. 158—160° (Found: C, 74·5; H, 5·2; N, 9·0. $C_{19}H_{16}O_2N_2$ requires C, 75·0; H, 5·3; N, 9·2%). When 4-amino-2-phenylquinoline was boiled with excess of acetoacetic ester for 30—60 min. the sole product isolated was a compound which crystallised from aqueous acetone or pyridine in plates, m. p. 256—258° (Found: C, 79·9; H, 5·45; N, 7·6%), and was unaffected by concentrated sulphuric acid at 100°.

*10-Phenyl-4 : 9-diazaphenanthrene.*—A mixture of 4-amino-2-phenylquinoline (10 g.), arsenic pentoxide (10 g.), glycerol (20 g.), and concentrated sulphuric acid (20 g.) was heated at 145—155° for 5 hr. The resinous product was extracted successively with boiling water (250 ml.) and hot 2N-sulphuric acid (3 × 200 ml.). The combined extracts were basified and the precipitate was filtered off, washed, dried, and extracted with hot benzene (charcoal). The extracts were evaporated, giving *10-phenyl-4 : 9-diazaphenanthrene* (3·2 g.; m. p. 140—145°), which separated from methanol in prisms, or from light petroleum (b. p. 80—100°) in needles, m. p. 144—145° (Found: C, 84·7; H, 4·8; N, 10·5. $C_{18}H_{12}N_2$ requires C, 84·3; H, 4·7; N,

[12] Buchman, McCloskey, and Seneker, *J. Amer. Chem. Soc.*, 1947, **69**, 380.
[13] Baker, Lappin, Albisetti, and Riegel, *ibid.*, 1946, **68**, 1267.
[14] Cf. Caldwell and Walls, *J.*, 1948, 188.
[15] John, *Ber.*, 1926, **59**, 1447.

XUM

10·9%). The 9-*methiodide* (II) separated from chloroform in bright yellow plates (becoming orange on drying), m. p. 193° (decomp.) (Found: N, 6·6; I, 31·9. $C_{19}H_{15}N_2I$ requires N, 7·0; I, 31·9%). Treatment of the methiodide with aqueous ammonia and crystallisation of the product from benzene gave 9 : 10-*dihydro*-10-*hydroxy*-9-*methyl*-10-*phenyl*-4 : 9-*diazaphenanthrene* (IV), decomp. >148° (Found: C, 78·7; H, 5·7. $C_{19}H_{16}ON_2$ requires C, 79·1; H, 5·6%), also obtained by boiling the methiodide (0·1 g.) with potassium ferricyanide (0·3 g.) and 2N-sodium hydroxide (2 ml.) in water (10 ml.) for 20 min. Solutions of the pseudo-base exhibited blue fluorescence.

2-m-*Nitrophenylquinoline*-4-*carboxylic Acid*.—90% Pyruvic acid (6·6 g.) in ethanol (20 ml.) was added during 10 min. to a refluxing solution of aniline (6 g.) and *m*-nitrobenzaldehyde (10 g.) in ethanol (30 ml.). After a further 1·5 hr. the solution was cooled and filtered. Recrystallisation of the precipitate from acetic acid gave the acid (2·45 g.; 13%), m. p. 264—265° (Found: N, 9·4. Calc. for $C_{16}H_{10}O_4N_2$: N, 9·5%) (lit.,[11] m. p. 260°). A similar preparation using *p*-nitrobenzaldehyde yielded 2-*p*-nitrophenylquinoline-4-carboxylic acid (6%) m. p. 260—262° (decomp.) (Found: C, 65·2; H, 3·15; N, 9·6. Calc. for $C_{16}H_{10}O_4N_2$: C, 65·3; H, 3·4; N, 9·5%) (lit.,[11] m. p. 255—256°).

*Nitration of* 2-*Phenylquinoline*-4-*carboxylic Acid*.—The acid (200 g.) was slowly added to nitric acid (*d* 1·5; 500 ml.), stirred and cooled so that the temperature remained <30°. After 30 min., the solution was poured into water (4 l.) and the pH was adjusted to 5 with aqueous ammonia. The solid was filtered off, washed with water, and crystallised from acetic acid (4—6 l.), giving a mixture (122—154 g., 51—65%), m. p. 225—227°, of principally the 2-*m*- and the 2-*p*-nitrophenyl compound. No separation was achieved by recrystallisation from acetic acid, butanol, acetone, or dimethylformamide.

4-*Ethoxycarbonylamino*-2-m-*nitrophenylquinoline*.—(*a*) 2-*m*-Nitrophenylquinoline-4-carboxylic acid (0·8 g.; prepared from *m*-nitrobenzaldehyde) was refluxed with excess of thionyl chloride for 3 hr. and the solution was evaporated. The residue was triturated with ether and filtered, and the solid was suspended in acetone and treated with excess of aqueous sodium azide. After 5 min., sodium hydrogen carbonate solution was added and the azide was filtered off, washed with water, and dissolved in chloroform. The washed and dried chloroform solution was then slowly added to boiling absolute ethanol, the chloroform being continuously removed through a short column. The ethanol solution was boiled for 30 min., then concentrated, cooled, and filtered. Crystallisation of the product from chloroform gave the *urethane* in needles, m. p. 202—204° (Found: C, 63·3; H, 4·5; N, 12·8. $C_{18}H_{15}O_4N_3$ requires C, 64·1; H, 4·5; N, 12·5%).

8-Nitro-2-phenylquinoline-4-carboxylic acid [12] similarly gave 4-*ethoxycarbonylamino*-8-*nitro*-2-*phenylquinoline* (41%), needles, m. p. 200° (Found: C, 64·0; H, 4·3; N, 12·5. $C_{18}H_{15}O_4N_3$ requires C, 64·1; H, 4·5; N, 12·5%), from ethanol or chloroform.

(*b*) The mixture (80 g.) of acids obtained by nitration of 2-phenylquinoline-4-carboxylic acid was similarly converted into the urethane. Crystallisation of the product from chloroform gave the *m*-nitro-urethane (22·65 g., 27%), m. p. 196—198°, raised by recrystallisation to 203—204° (not depressed on admixture with an authentic specimen). Evaporation of the mother-liquors and repeated crystallisation of the residue from acetone gave a small amount of 4-*ethoxycarbonylamino*-2-p-*nitrophenylquinoline* in needles, m. p. 197—198° (Found: C, 64·3; H, 4·55; N, 12·6. $C_{18}H_{15}O_4N_3$ requires C, 64·1; H, 4·5; N, 12·5%), depressed to <180° by the *m*-isomer but not depressed by a specimen, m. p. 195—197°, prepared from the authentic *p*-nitro-acid.

(*c*) The mixed nitro-acids (25 g.) were converted into the ethyl ester (24·6 g.), m. p. 95—98° (Found: C, 67·0; H, 4·4; N, 8·55. Calc. for $C_{18}H_{14}O_4N_2$: C, 67·0; H, 4·4; N, 8·7%), from acetone–50% ethanol. The mixed esters (30 g.) and hydrazine hydrate (7·1 g.) in pentan-1-ol (120 ml.) were refluxed for 20 hr. The hydrazide (19·5 g.), after crystallisation from ethanol, had m. p. 242—245° (Found: C, 62·2; H, 4·25; N, 17·8. Calc. for $C_{16}H_{12}O_3N_4$: C, 62·3; H, 3·9; N, 18·2%). A solution of this hydrazide (20 g.) in 0·68N-hydrochloric acid (95 ml.) and acetic acid (210 ml.) was stirred and cooled to 10°. 0·5N-Sodium nitrite (130 ml.) was added dropwise and the mixture was stirred for a further 0·75 hr. and diluted with water. The precipitated azide was converted into the urethane as previously described, giving 6·35 g. of *m*-nitrophenyl isomer, m. p. 200° (softens 194°) (Found: C, 63·8; H, 4·7; N, 12·7%).

Ethyl 8-nitro-2-phenylquinoline-4-carboxylate [12] similarly yielded successively the *hydrazide* (87%), m. p. 226—228° (Found: C, 62·4; H, 4·1; N, 17·5. $C_{16}H_{12}O_3N_4$ requires C, 62·3; H, 3·9; N, 18·2%), and the urethane (32%), m. p. 202—204°.

2-m-*Aminophenyl*-4-*ethoxycarbonylaminoquinoline*.—The nitro-compound was reduced over Raney nickel in ethanol. The *amine* separated from chloroform–light petroleum (b. p. 40—60°) in needles, m. p. 180—181° (Found: C, 69·9; H, 5·8; N, 13·7. $C_{18}H_{17}O_2N_3$ requires C, 70·3; H, 5·6; N, 13·7%). The *acetyl* derivative formed needles, m. p. 191—192° (Found: N, 11·8. $C_{20}H_{19}O_3N_3$ requires N, 12·0%), from chloroform.

4-*Amino*-2-m-*nitrophenylquinoline* (VIII).—A mixture of 4-ethoxycarbonylamino-2-*m*-nitrophenylquinoline (16 g.) and concentrated hydrochloric acid (400 ml.) was refluxed overnight, then cooled, and the hydrochloride was filtered off. A suspension of the hydrochloride in dilute aqueous sodium hydroxide was stirred for 15 min. at 100°, cooled, and filtered. Crystallisation of the product from aqueous acetone gave the *amine* (11·25 g., 89%; m. p. 296°) which formed needles or plates, m. p. either 206—208° or 304—306° (melts and resolidifies <200°) (Found: C, 68·1; H, 4·4; N, 15·85. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·2; N, 15·85%), from ethanol or chloroform.

Similar hydrolysis of 4-ethoxycarbonylamino-8-nitro-2-phenylquinoline gave 4-*amino*-8-*nitro*-2-*phenylquinoline* (IX) (78%), yellow prisms (from chloroform) or plates (from aqueous acetone), m. p. 144—146° (Found: C, 67·8; H, 4·2; N, 15·5. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·2; N, 15·85%). The *hydrochloride*, yellow prisms from ethanol, decomposed at 290—300° (Found: C, 59·5; H, 4·1; N, 13·4; Cl, 11·7. $C_{15}H_{11}O_2N_3$,HCl requires C, 59·7; H, 4·0; N, 13·9; Cl, 11·8%).

*Condensation of* 4-*Aminoquinolines with Ethoxymethylenemalonic ester*.—(*a*) A solution of 4-amino-2-phenylquinoline (15 g.) and ethoxymethylenemalonic ester (17 g.) in xylene (200 ml.) was boiled for 3·5 hr. The residue obtained on evaporation under reduced pressure was crystallised from ethanol, giving *diethyl* (2-*phenyl*-4-*quinolylaminomethylene*)*malonate* (XIV) (19·2 g.; m. p. 118—122°) in rectangular plates, m. p. 123—124° (Found: C, 70·6; H, 5·7; N, 7·1. $C_{23}H_{22}O_4N_2$ requires C, 70·8; H, 5·7; N, 7·2%). In a similar experiment (but using only 15 g. of ester and boiling for 6 hr.) there was obtained in addition to the above ester (12·6 g.; m. p. 120—123°) an ethanol-insoluble compound (5 g., m. p. 237—240°), probably *ethyl* β-(2-*phenyl*-4-*quinolylamino*)-α-(2-*phenyl*-4-*quinolylcarbamoyl*)*acrylate* (X), which separated from chloroform in long prisms, m. p. 238—239° (Found : C, 75·3; H, 4·9; N, 9·6. $C_{36}H_{28}O_3N_4,0{\cdot}5H_2O$ requires C, 75·4; H, 5·1; N, 9·8%). Cyclisation of this compound is described below.

(*b*) A similar condensation, using 4-amino-2-*m*-nitrophenylquinoline, yielded *ethyl* β-(2-m-*nitrophenyl*-4-*quinolylamino*)-α-(2-m-*nitrophenyl*-4-*quinolylcarbamoyl*)*acrylate* (XI), prisms, m. p. 276° (decomp.) (Found: N, 12·9. $C_{36}H_{26}O_7N_6$ requires N, 12·8%), from ethanol, and *diethyl* (2-m-*nitrophenyl*-4-*quinolylaminomethylene*)*malonate* (XV), prisms, m. p. 180—182° (softens 176°) (Found: N, 9·7. $C_{23}H_{21}O_6N_3$ requires N, 9·65%), from ethanol.

(*c*) 4-Aminoquinaldine likwise gave *diethyl* 2-*methyl*-4-*quinolylaminomethylenemalonate*, m. p. 103—105° (Found: C, 66·1; H, 6·1; N, 8·75. $C_{18}H_{20}O_4N_2$ requires C, 65·8; H, 6·2; N, 8·5%), from ethanol.

*Cyclisation of the Aminomethylenemalonic Esters to* 4 : 9-*Diazaphenanthrenes*.—(*a*) Diethyl (2-phenyl-4-quinolylaminomethylene)malonate (XIV) (12·6 g.) was boiled with Dowtherm for 15 min. The cooled solution was diluted with light petroleum (b. p. 40—60°), and the precipitate was collected and recrystallised from benzene–light petroleum (b. p. 40—60°), yielding *ethyl* 1-*hydroxy*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate* (XVI) (10·6 g.; m. p. 235—240°), which formed blades, m. p. 252—254° (Found: C, 72·8; H, 4·8; N, 8·1. $C_{21}H_{16}O_3N_2$ requires C, 73·3; H, 4·7; N, 8·1%), from ethanol.

(*b*) Diethyl 2-methyl-4-quinolylaminomethylenemalonate similarly gave *ethyl* 1-*hydroxy*-10-*methyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate*, m. p. 208—210° (Found: C, 66·2; H, 5·4; N, 10·0. $C_{16}H_{14}O_3N_2,0{\cdot}5H_2O$ requires C, 66·0; H, 5·2; N, 9·6%).

- *Direct Formation of* 4 : 9-*Diazaphenanthrenes from* 4-*Aminoquinolines and Ethoxymethylenemalonic Ester*.—(*a*) A solution of 4-amino-2-phenylquinoline (11 g.) and ethoxymethylenemalonic ester (10·8 g.) in Dowtherm (150 ml.) was heated at 130° for 1 hr., then boiled for 30 min., cooled, and diluted with light petroleum (b. p. 40—60°). Next morning the precipitate was collected and repeatedly crystallised from ethanol and from benzene–light petroleum (b. p. 40—60°), giving the diazaphenanthrene (XVI) (6·7 g.; m. p. 240—248°) together with a sparingly soluble compound (2·3 g.), probably 1-*hydroxy*-10-*phenyl*-2-(2-*phenyl*-4-*quinolylcarbamoyl*)-4 : 9-*diazaphenanthrene* (XII), which separated from pyridine in needles, m. p. 345—348° (decomp.) (Found: C, 77·5; H, 4·8; N, 10·4. $C_{34}H_{22}O_3N_4,0{\cdot}5H_2O$ requires C, 77·3; H, 4·4; N, 10·6%). The same compound was formed by cyclisation in Dowtherm of the

corresponding acrylate, m. p. 238—239°, described above. It was unaffected when boiled for several hours with concentrated hydrochloric acid or sodium hydroxide, but yielded an amorphous *chloro-derivative* (Found: Cl, 5·8. $C_{34}H_{21}ON_4Cl$ requires Cl, 6·6%) with phosphorus oxychloride.

(*b*) After a similar experiment with 4-amino-2-*m*-nitrophenylquinoline (but boiling for 10 min.), the precipitate was collected, dissolved in chloroform, and filtered from 1-*hydroxy*-10-m-*nitrophenyl*-2-(2-m-*nitrophenyl*-4-*quinolylcarbamoyl*)-4 : 9-*diazaphenanthrene* (XIII), prisms, decomp. 345° (Found: C, 66·75; H, 3·4; N, 13·4. $C_{34}H_{20}O_6N_6$ requires C, 67·1; H, 3·3; N, 13·8%), which could not be satisfactorily recrystallised. The chloroform solution was filtered through a short column of alumina, which was washed with more solvent. The combined filtrates were concentrated and diluted with light petroleum (b. p. 40—60°), yielding *ethyl* 1-*hydroxy*-10-m-*nitrophenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate* (XVII) (56%), which formed prisms, m. p. 284—286° (decomp.) (Found: C, 63·8; H, 3·8; N, 10·3. $C_{21}H_{15}O_5N_3,0·5H_2O$ requires C, 63·7; H, 4·1; N, 10·6%), from ethanol. In other experiments the yield varied from 50 to 89%.

(*c*) 4-Amino-8-nitro-2-phenylquinoline likewise yielded *ethyl* 1-*hydroxy*-8-*nitro*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate* (XVIII) (72%), which after chromatography in benzene and recrystallisation from chloroform–benzene formed plates, m. p. 290—292° (decomp.) (Found: C, 65·1; H, 3·7; N, 10·9. $C_{21}H_{15}O_5N_3$ requires C, 64·7; H, 3·9; N, 10·8%). The pure nitro-compound is sparingly soluble in benzene. Reduction of the nitro-compound over platinum oxide in ethyl acetate, or Raney nickel in ethanol, and crystallisation of the product from chloroform–ether, gave *ethyl* 8-*amino*-1-*hydroxy*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate*, m. p. 274—276° (decomp.) (Found: N, 12·0. $C_{21}H_{17}O_3N_3$ requires N, 11·7%).

(*d*) In a similar experiment with 4-aminoquinaldine, the only product isolated was 1-*hydroxy*-10-*methyl*-2-(2-*methyl*-4-*quinolylcarbamoyl*)-4 : 9-*diazaphenanthrene* which formed yellow needles, m. p. >320° (Found: C, 68·7; H, 4·9; N, 13·7. $C_{24}H_{18}O_2N_4,1·5H_2O$ requires C, 68·4; H, 5·0; N, 13·3%), from pyridine.

*Hydrolysis of* 4 : 9-*Diazaphenanthrene*-2-*carboxylic Esters and Thermal Decarboxylation of the Derived Acids.*—(*a*) Ethyl 1-hydroxy-10-phenyl-4 : 9-diazaphenanthrene-2-carboxylate (5·65 g.) was boiled with 2N-sodium hydroxide (100 ml.) for 2 hr. The hot solution was filtered (charcoal) and the filtrate was acidified with acetic acid. The precipitated 2-*carboxylic acid* (4·7 g., 91%) was washed with boiling water and dried. An analytical specimen, recrystallised from nitrobenzene, had m. p. >360° (Found: C, 71·9; H, 3·9; N, 9·0. $C_{19}H_{12}O_3N_2$ requires C, 72·2; H, 3·8; N, 8·9%). The foregoing acid (11·1 g.) was slowly added to boiling Dowtherm (400 ml.), boiling being continued until a clear solution was obtained (0·75—1 hr.). 1-*Hydroxy*-10-*phenyl*-4 : 9-*diazaphenanthrene* (XIX) (9·2 g., 96%), which crystallised from the cooled solution, was filtered off, washed with benzene and ether, and dried. It was pure enough for chlorination. A specimen recrystallised from ethanol formed prisms, m. p. >340° (Found: C, 79·3; H, 4·5; N, 10·1. $C_{18}H_{12}ON_2$ requires C, 79·5; H, 4·5; N, 10·3%). The *hydrochloride* separated from a mixture of acetic and 2N-hydrochloric acid in prisms, m. p. 345—346° (decomp.) (Found: N, 9·3; Cl, 11·7. $C_{18}H_{12}ON_2,HCl$ requires N, 9·1; Cl, 11·5%).

(*b*) 1-Hydroxy-10-*m*-nitrophenyl-4 : 9-diazaphenanthrene-2-carboxylic acid (60—80%; used without purification) and 1-*hydroxy*-10-m-*nitrophenyl*-4 : 9-*diazaphenanthrene* (73—88%), m. p. 334—336° (decomp.) (Found: C, 68·0; H, 3·8; N, 13·1. $C_{18}H_{11}O_3N_3$ requires C, 68·1; H, 3·5; N, 13·25%), were similarly obtained.

*Formation of* 1-*Amino*-4 : 9-*diazaphenanthrenes from* 1-*Hydroxy*-4 : 9-*diazaphenanthrenes* via *the* 1-*Chloro-derivatives.*—(*a*) 1-Hydroxy-10-phenyl-4 : 9-diazaphenanthrene (2·05 g.) was boiled with phosphorus oxychloride (15 ml.) for 15 min. The residue obtained after removal of excess of reagent *in vacuo* was treated with dilute aqueous sodium hydroxide, and the precipitate (1·9 g., 87%; m. p. >170°) was collected, washed, and dried. Recrystallisation from ethanol gave 1-*chloro*-10-*phenyl*-4 : 9-*diazaphenanthrene* (XX) in needles, m. p. 176—178° (Found: N, 9·3; Cl, 12·2. $C_{18}H_{11}N_2Cl$ requires N, 9·6; Cl, 12·2%). The *metho*(*methyl sulphate*), prepared in boiling toluene and purified from methanol–ether, had m. p. 170—180° (decomp.) (Found: N, 6·7. $C_{20}H_{17}O_4N_2ClS$ requires N, 6·7%). A solution of the chloro-compound (5 g.) in phenol (50 g.) was heated at 180—200° while a rapid stream of ammonia was passed in for 7·5 hr. After the removal of phenol by steam-distillation the solution was basified and the precipitate was filtered off, washed, and dried. Crystallisation of the product from benzene gave 1-*amino*-10-*phenyl*-4 : 9-*diazaphenanthrene* (XXI) (4·1 g., 88%; m. p. 218—220°) which separated from

ethanol in plates, m. p. 224° (Found: C, 79·7; H, 5·4; N, 15·3. $C_{18}H_{13}N_3$ requires C, 79·7; H, 4·8; N, 15·5%). The *hydrochloride* had m. p. 294—295° (Found: N, 13·1; Cl, 11·9. $C_{18}H_{13}N_3$,HCl requires N, 13·6; Cl, 11·6%). The *methiodide* (89%) formed yellow prisms, m. p. 236—238° (decomp.) (Found: N, 10·2; I, 30·7. $C_{19}H_{16}N_3I$ requires N, 10·2; I, 30·7%). Treatment of the methiodide with aqueous ammonia and purification of the precipitate from benzene–light petroleum (b. p. 40—60°) gave 1-*amino*-9 : 10-*dihydro*-10-*hydroxy*-9-*methyl*-10-*phenyl*-4 : 9-*diazaphenanthrene* (V), an amorphous solid, decomp. >90° (Found: N, 14·0. $C_{19}H_{17}ON_3$ requires N, 13·9%), which showed strong green fluorescence in solution. When the methiodide (0·5 g.) in water (50 ml.) was boiled for 15 min. with potassium ferricyanide (1·5 g.) and 2N-sodium hydroxide (10 ml.), and the insoluble product was purified from benzene–light petroleum and sublimed at 180°/0·05 mm., 1-*amino*-9 : 10-*dihydro*-9-*methyl*-10-*oxo*-4 : 9-*diazaphenanthrene* (VI) was obtained as prisms, m. p. 178—179° (Found: C, 68·7; H, 4·85; N, 18·6. $C_{13}H_{11}ON_3$ requires C, 69·3; H, 4·9; N, 18·7%).

(*b*) 1-*Chloro*-10-m-*nitrophenyl*-4 : 9-*diazaphenanthrene* (XXIII), similarly prepared (67%), formed prisms, m. p. 216—219° (Found: N, 12·5; Cl, 10·6. $C_{18}H_{10}O_2N_3Cl$ requires N, 12·5; Cl, 10·6%), from chloroform–light petroleum (b. p. 40—60°). A suspension of 1-chloro-10-*m*-nitrophenyl-4 : 9-diazaphenanthrene (3·2 g.) and Raney nickel in warm ethanol (200 ml.) was shaken with hydrogen. When the theoretical uptake had occurred (3·25 hr.) the suspension was filtered and the catalyst was washed with chloroform. The combined filtrates were evaporated and a solution of the residue in chloroform was filtered through alumina (to remove by-product; see below), concentrated, and diluted with ether, giving 10-m-*aminophenyl*-1-*chloro*-4 : 9-*diazaphenanthrene* (2·25 g., 77%) in prisms, m. p. 202—204° (Found: N, 13·75; Cl, 11·7. $C_{18}H_{12}N_3Cl$ requires N, 13·7; Cl, 11·7%). When the reduction was carried out over platinum oxide, a considerable amount of 10-m-*aminophenyl*-4 : 9-*diazaphenanthrene hydrochloride* (XXV), prisms (from ethanol), m. p. >360° (Found: N, 12·5; Cl, 11·15. $C_{18}H_{13}N_3$,HCl,$H_2O$ requires N, 12·9; Cl, 10·9%), was formed as by-product.

10-*m*-Aminophenyl-1-chloro-4 : 9-diazaphenanthrene was aminated in the usual way. Crystallisation of the product from chloroform gave 1-*amino*-10-m-*aminophenyl*-4 : 9-*diazaphenanthrene* (XXVI) (97%, m. p. 233—234°) which formed prisms, m. p. 221° and 236—238° (Found: C, 75·1; H, 4·85; N, 19·7. $C_{18}H_{14}N_4$ requires C, 75·5; H, 4·9; N, 19·6%), from benzene. The base formed a *trihydrochloride* (Found: N, 14·0; Cl, 27·6. $C_{18}H_{14}N_4$,3HCl requires N, 14·2; Cl, 27·0%) and a *diacetyl* derivative, which separated from ethanol in rhombs, m. p. 288—290° (Found: C, 71·0; H, 5·45; N, 14·8. $C_{22}H_{18}O_2N_4$ requires C, 71·3; H, 4·9; N, 15·1%). The diacetyl derivative with excess of methyl iodide gave the 9-*methiodide* (84%), which formed yellow prisms, m. p. 284—286° (Found: N, 10·9; I, 23·6. $C_{23}H_{21}O_2N_4I$ requires N, 10·9; I, 24·8%), from methanol–ether.

(*c*) *Ethyl* 1-*chloro*-8-*nitro*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate* (93%) formed needles, m. p. 182° (Found: N, 9·9; Cl, 8·35. $C_{21}H_{14}O_4N_3Cl$ requires N, 10·3; Cl, 8·7%), from chloroform–ether. It was converted into *ethyl* 1-*amino*-8-*nitro*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate* (75%) which was crystallised from chloroform–light petroleum, giving needles, m. p. 217—219° (Found: C, 65·25; H, 4·35; N, 14·5. $C_{21}H_{16}O_4N_4$ requires C, 64·95; H, 4·2; N, 14·4%).

1-*Phenoxy*-10-*phenyl*-4 : 9-*diazaphenanthrene* (XXII).—Ammonia was passed for 3·5 hr. into a solution of 1-chloro-10-phenyl-4 : 9-diazaphenanthrene (1·75 g.) in phenol (10 g.) maintained at 180°. The product, isolated in the usual way, was crystallised twice from ethanol, giving the *phenoxy-compound* (0·6 g.) in long prisms, m. p. 182° (Found: C, 81·1; H, 4·6; N, 8·1. $C_{24}H_{16}ON_3$,0·5$H_2O$ requires C, 80·7; H, 4·8; N, 7·8%). From the mother-liquors was obtained some of the amino-compound, m. p. 224°.

10-m-*Nitrophenyl*-1-*phenoxy*-4 : 9-*diazaphenanthrene* (XXIV).—The 1-chloro-compound (0·6 g.) in phenol (10 g.) at 190—200° was treated with ammonia for 5·5 hr. and the product was isolated in the usual way. The 1-*phenoxy-compound* (0·25 g.; m. p. 168—170°) formed prisms, m. p. 177—179° (Found: N, 10·6. $C_{24}H_{15}O_3N_3$ requires N, 10·7%), on recrystallisation from aqueous ethanol and from benzene.

1-*Amino*-10-m-*aminophenyl*-4 : 9-*diazaphenanthrene* 9-*Methiodide* (XXXIV).—1-Acetamido-10-*m*-acetamidophenyl-4 : 9-diazaphenanthrene methiodide (1·1 g.) was refluxed with concentrated hydrochloric acid (20 ml.) for 4 hr. and the solution was evaporated *in vacuo*. A solution of the residue in hot water was filtered (charcoal), adjusted to pH 7 with sodium hydrogen carbonate, treated with sodium iodide, and cooled. The *methiodide* (0·8 g.)

XUM

was filtered off, washed with a little cold water, and crystallised from methanol–ether (Found: N, 12·45; I, 27·8. $C_{19}H_{17}N_4I,H_2O$ requires N, 12·55; I, 28·4%).

1-*Amino*-10-m-*dimethylaminophenyl*-4 : 9-*diazaphenanthrene* 3′ : 9-*Dimethiodide* (XXXIII).—A mixture of 1-amino-10-*m*-aminophenyl-4 : 9-diazaphenanthrene (1·19 g.), anhydrous sodium carbonate (0·44 g.), and methyl iodide (30 ml.) in methanol (30 ml.) was refluxed for 20 hr., concentrated, cooled, and filtered. The *dimethiodide* (1·2 g., 48%) separated from methanol in irregular prisms (Found: N, 9·6; I, 42·0. $C_{22}H_{24}N_4I_2$ requires N, 9·4; I, 42·4%).

1-*Ethoxycarbonylamino*-10-m-*ethoxycarbonylaminophenyl*-4 : 9-*diazaphenanthrene* 9-*Methiodide*.—A mixture of 1-amino-10-*m*-aminophenyl-4 : 9-diazaphenanthrene (1 g.), ethyl chloroformate (1 g.) and diethylaniline (1·2 g.) in dry ethanol (50 ml.) was refluxed for 2 hr. and evaporated, and the residue was diluted with water, basified with ammonia, and extracted with chloroform. The dried extract was filtered through alumina, the filtrate was evaporated, and the residue was triturated with light petroleum (b. p. 40—60°). The amorphous product (1 g.) was heated with methyl iodide at 110°, yielding the *methiodide* (XXXV) (0·6 g.), decomp. 190—200° (Found: I, 21·8. $C_{25}H_{35}O_4N_4I$ requires I, 22·2%).

1 : 8-*Diamino*-2-*ethoxycarbonyl*-10-*phenyl*-4 : 9-*diazaphenanthrene* (XXIX).—The 8-nitro-compound was reduced catalytically (Raney nickel) in ethanol, giving the *diamine* (84%) as yellow rhombs, m. p. 213° (Found: N, 15·4. $C_{21}H_{18}O_2N_4$ requires N, 15·6%), from ethanol. The *hydrochloride* formed orange rhombs (Found: N, 12·8; Cl, 12·7. $C_{21}H_{18}O_2N_4,1·5HCl,H_2O$ requires N, 13·0; Cl, 12·4%). The 8-*acetyl derivative* (XXX), prepared by treatment with acetic anhydride–pyridine at 90°, formed needles, m. p. 207—208° or 233—235° (Found: C, 69·0; H, 5·2; N, 14·0. $C_{23}H_{20}O_3N_4$ requires C, 69·0; H, 5·0; N, 14·0%), from chloroform–light petroleum (b. p. 40—60°). The 8-*ethoxycarbonyl derivative* (XXXI) (1·1 g., 92%), prepared by refluxing a mixture of the diamine (1 g.), ethyl chloroformate (0·5 g.), and diethylaniline (0·6 g.) in dry ethanol (50 ml.) for 1 hr., separated from chloroform–ethanol in needles, m. p. 200° (Found: C, 66·5; H, 4·95; N, 12·9; OEt, 20·8. $C_{24}H_{22}O_4N_4$ requires C, 66·9; H, 5·2; N, 13·0; OEt, 20·9%). Its *hydrochloride* crystallised from ethanol in plates, m. p. 248—250° (decomp.) (Found: N, 11·95; Cl, 7·45. $C_{24}H_{23}O_4N_4,HCl$ requires N, 12·0; Cl, 7·6%).

1 : 8-*Diamino*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylic acid*, obtained by hydrolysis of the corresponding ethyl ester, formed yellow needles, m. p. 286° (decomp.) (Found: C, 68·6; H, 4·5; N, 16·4. $C_{19}H_{14}O_2N_4,0·25H_2O$ requires C, 68·1; H, 4·2; N, 16·7%), from aqueous ethanol.

*Ethyl* 1-*Amino*-8-*dimethylamino*-10-*phenyl*-4 : 9-*diazaphenanthrene*-2-*carboxylate* 8 : 9-*Dimethiodide* (XXVIII).—Ethyl 1 : 8-diamino-10-phenyl-4 : 9-diazaphenanthrene-2-carboxylate (0·716 g.), sodium carbonate (0·212 g.), excess of methyl iodide, and methanol were refluxed for 18 hr., then evaporated. The residue was triturated with acetone and filtered, and the solid crystallised from methanol, giving the *dimethiodide* (1·25 g., 93%) in yellow prisms, m. p. 150—152° (decomp.) (Found: N, 8·35; I, 38·5. $C_{25}H_{28}O_2N_4I_2$ requires N, 8·35; I, 37·9%).

The author thanks Dr. A. J. Ewins, F.R.S., and Dr. J. N. Ashley, F.R.I.C., for their interest and encouragement, Mr. S. Bance, B.Sc., A.R.I.C., for the semimicro-analyses, and the Directors of May and Baker Ltd. for permission to publish these results.

The Research Laboratories, May and Baker Ltd.,
Dagenham, Essex.

[*Received, October 2nd*, 1957.]

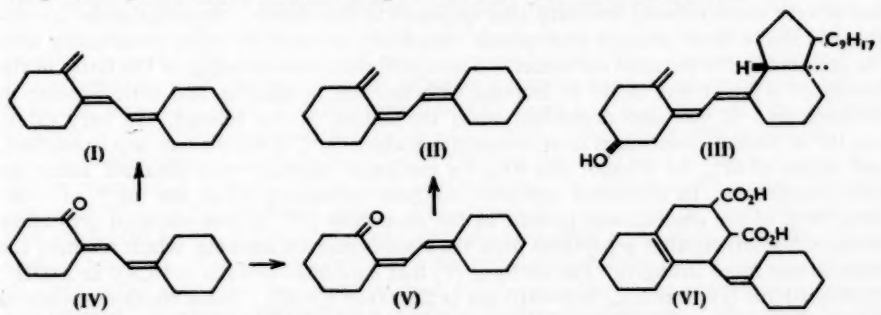
## 162. *Calciferol and its Relatives. Part III.* Partial Synthesis of Calciferol and of* epi*Calciferol.*[1]

By I. T. Harrison and B. Lythgoe.

The *cis*-triene (II), a simple model for calciferol, has been prepared from the *cis*-dienone (V), obtained by photoisomerisation of the *trans*-dienone (IV). By extending the method, calciferol and *epi*calciferol have been obtained in a partial synthesis from the aldehyde (VII).

Two main difficulties impede synthesis of calciferol; they arise from the semicyclic disposition of the three conjugated double bonds and from the *cis*-configuration of the central member. We have attempted in this series to overcome these difficulties separately in model synthetic work, aiming first at the trisemicyclic *trans*-triene (I), and later at the *cis*-isomer (II) which contains essentially the same conjugated system as calciferol (III). If these model studies were successful it seemed unlikely that their extension to provide for the special features of the vitamin (hydroxyl group and bicyclic CD-system) would meet major difficulties.

Completion of experiments leading to the *trans*-triene (I) has been reported.[2,*] The triene was first * obtained by established elimination methods of forming the double bonds, but the advent of Wittig and Schöllkopf's [3] reaction provided an alternative method of constructing semicyclic double bonds which was clearly to be of great value in the present field. We applied this reaction to construct the central double bond of the triene (I) in a synthesis [2] using 2-dimethylaminomethyl*cyclo*hexanone as the ketonic starting material, and also to construct the terminal methylene double bond in a further synthesis using the *trans*-dienone (IV) as the ketonic component. The last is the most effective of the three available methods. Inhoffen and his associates [4] have also used the Wittig reaction independently in related work, some aspects of which are referred to below.




The above methods give exclusively trienes with the *trans*-configuration; the problem of securing a central *cis*-double bond remained for study. We have obtained solutions by two very different methods, which are reported in this and the following paper. The present paper describes the simpler of the two methods in its application to a synthesis of the *cis*-triene (II) and also to a partial synthesis of calciferol.

The most desirable intermediate for a synthesis of the *cis*-triene (II) was clearly the *cis*-dienone (V). Few chemical methods for the preparation of *cis*-αβ-unsaturated ketones have been reported in the literature. The semihydrogenation of acetylenic ketones, used

* Part II, Lythgoe, Trippett, and Watkins, *J.*, 1956, 4060.

[1] A preliminary report appeared in *Proc.*, 1957, 261.

[2] Harrison, Lythgoe, and Trippett, *Chem. and Ind.*, 1955, 507; *J.*, 1955, 4016.

[3] Wittig and Schöllkopf, *Chem. Ber.*, 1954, **87**, 1318.

[4] Inhoffen, Kath, Sticherling, and Brückner, *Annalen*, 1957, **603**, 25; cf. *Angew. Chem.*, 1955, **67**, 276.

XUM

recently by Schinz and his colleagues,[5] is inapplicable to the present case. On a few occasions a *cis*-αβ-unsaturated ketone has been obtained as the product of an aldol condensation; an example is the formation of a *cis*-*p*-methoxybenzylidene derivative from 6-methoxy-1-tetralone.[6] Reaction [7] of *cyclo*hexanone and *cyclo*hexylideneacetaldehyde gives the *trans*-dienone (IV), its *trans*-nature being shown by its conversion into the *trans*-triene (I); we varied the conditions of the aldol condensation in attempts to isolate some *cis*-dienone, but without success.

On the other hand, *cis*-αβ-unsaturated ketones have long been known as irradiation products of the *trans*-isomers. Paal and Schulze [8] recorded an early example in the quantitative isomerisation of dibenzoylethylene to its *cis*-isomer by sunlight, and more recently Lutz and Jordan [9] found that irradiation of *trans*-benzylideneacetophenone gave an equilibrium mixture in which the *cis*-form predominated (74%). Büchi and Yang [10] have shown that the *trans*-dienones crotonylideneacetone and β-ionone also undergo the reaction, although the geometric inversion of β-ionone is complicated by cyclisation of the *cis*-form to a pyran derivative. We therefore attempted the photochemical isomerisation of the *trans*-dienone (IV).

The less stable *cis*-forms of αβ-unsaturated ketones are usually, although not invariably, isomerised rapidly to the *trans*-forms when treated with mineral acids at room temperature. They are also differentiated from the *trans*-forms by their light absorption; the *cis*-form may absorb maximally at either shorter [9] or longer [5] wavelengths than the *trans*-form according to the particular structure present, but the intensity of absorption is always much lower for a *cis*-form. These criteria were used to detect isomerisation of the *trans*-dienone (IV) and later to determine its extent under different conditions. Sunlight and ultraviolet light from an unshielded mercury-vapour lamp decomposed the dienone; the observed spectral changes were incompletely reversed by the addition of acid to the solutions. The most suitable light source was a shielded lamp with main emission near 365 mμ. Solutions of the dienone (IV) showed absorption of slightly reduced wavelength and of very much reduced intensity after exposure to this source; moreover under favourable conditions these changes were almost completely reversed by acids, consistently with the presence of the required *cis*-isomer. The equilibrium concentration of the latter in the irradiated solution was found to increase with increase in dilution and with decrease in temperature; it was also dependent upon the nature of the solvent. In very dilute (*ca.* $10^{-5}$M) benzene solution at room temperature about 50% of the dienone was isomerised, and values of 67% for ethanol and 80% for methanol solutions were obtained under the same conditions. In irradiated methanol solutions containing about 300 mg./l. at −60° some 90% of the dienone was present as the *cis*-isomer (V); it was obtained crystalline from such solutions after separation from the *trans*-isomer on alumina, which retained the *trans*-isomer more strongly. The *cis*-form (V) had $\lambda_{max.}$ 304—305 mμ (ε 15,200 in EtOH); the *trans*-form (IV) has $\lambda_{max.}$ 309—310 mμ (ε 22,500 in EtOH). Some *cis*-αβ-unsaturated ketones [5] give the semicarbazones of the *trans*-isomers when the normal procedure is used, free alcoholic semicarbazide being required in order to obtain the derivative of the *cis*-form, but the semicarbazone of the *cis*-dienone (V) was obtained by the normal procedure. When slowly heated it was transformed into the semicarbazone of the *trans*-isomer.

Reaction with methylenetriphenylphosphorane converted the *cis*-dienone (V) into the desired *cis*-triene (II), a rather unstable oil which decomposed in the presence of air at room temperature and also in its absence above 70°; the nature of the latter change merits investigation. The new triene required 3 mols. of hydrogen for saturation in the presence of palladium. Its $\lambda_{max.}$ 261 mμ (ε 17,000 in EtOH) differs somewhat from that of calciferol

[5] Theus, Surber, Colombi, and Schinz, *Helv. Chim. Acta*, 1955, **38**, 239.
[6] Bentley and Firth, *J.*, 1955, 2403.
[7] Dimroth, *Ber.*, 1938, **71**, 1346.
[8] Paal and Schulze, *Ber.*, 1902, **35**, 168.
[9] Lutz and Jordan, *J. Amer. Chem. Soc.*, 1950, **72**, 4090.
[10] Büchi and Yang, *J. Amer. Chem. Soc.*, 1957, **79**, 2318.

(265—266 mμ) in the same way as that of the *trans*-triene (I) (269—270 mμ) differs from that of 5 : 6-*trans*-calciferol [11] (XII) (272—273 mμ), these differences depending on the presence or absence of the bicyclic CD-system. The trisemicyclic structure of the triene (II) was shown by infrared bands near 852 (=CH), 891 ($=CH_2$), 1610, 1639, and 1653 (triene C=C) cm.$^{-1}$; similar bands occur in the spectrum of calciferol near 859, 887, 1610, 1634, and 1653 cm.$^{-1}$. The *cis*-triene, like calciferol, but unlike the *trans*-triene (I), was isomerised only slowly by dilute mineral acids. The relative speeds of reaction of the three compounds with maleic anhydride were approximately: *trans*-triene : *cis*-triene : calciferol = 6·9 : 1·3 : 1, this being the expected order of increasing steric hindrance to the reaction. The adduct so obtained from the *cis*-triene (II) was hydrolysed to the crystalline acid (VI), which is analogous to the dibasic acid similarly obtained from calciferol,[12] and stereoisomeric with that similarly obtained from the *trans*-triene [2] (I). These reactions demonstrate the *cis*-configuration of the new triene (II).

Means for extending the above work to a partial synthesis of calciferol were to hand. The bicyclic analogue (VII) of *cyclo*hexylideneacetaldehyde was first obtained by Heilbron, Spring, and their co-workers [13] in their degradation of the vitamin by chromic acid, and it is now readily obtained by Windaus and Riemann's method.[14] Inhoffen *et al.*[15] condensed this aldehyde with 4-acetoxy*cyclo*hexanone in the presence of sodium ethoxide and obtained a mixture, m. p. 141° (138°), of the $C_{(3)}$-epimers * of the conjugated dienone (VIII). They were aware of the possibility that the base might cause a change at $C_{(14)}$ to the more stable β(H)-configuration, and they obtained evidence [4] against it. We have repeated their preparation of the conjugated dienones (VIII) and our results confirm theirs in this respect. The product obtained by Inhoffen *et al.* may, however, have represented a different mixture of $C_{(3)}$-epimer from ours; they cite no optical rotation for their material. Our material (VIII) had m. p. 145°, $[\alpha]_D$ +165° (in $C_6H_6$), and proved later to contain an excess (*ca.* 3 : 1) of the 3α-epimer.

Whereas in the model dienone (IV) the symmetry of the terminal quaternary carbon atom of the unsaturated system confines geometric isomerism to the αβ-double bond, in the dienone (VIII) the βγ(or 7 : 8)-double bond may, in principle, also be isomerised. In practice, however, this bond was not affected. Irradiation of the dienone epimers (VIII) in methanol at −60° converted them virtually quantitatively, as shown by subsequent reactions, into the 5 : 6-*cis*-7 : 8-*trans*-epimers (IX) which had $\lambda_{max.}$ 310—311 mμ (ε 15,000 in EtOH); the all-*trans*-epimers (VIII) have $\lambda_{max.}$ 312—313 mμ (ε 25,000 in EtOH).

The ketonic oxygen atom in the epimers (IX) was replaced by a methylene group in a Wittig reaction; it is worth noting that such reactions are conveniently carried out without protection for the hydroxyl group. The ultraviolet absorption of the crude products was unaffected by the addition of dilute acid, showing their essential freedom from *trans*-trienoid material. Esterification with 3 : 5-dinitrobenzoyl chloride gave a readily separable mixture: after removal of the major product, which crystallised first, the minor component was isolated; it proved identical with calciferol 3 : 5-dinitrobenzoate. Hydrolysis readily gave the free crystalline vitamin (III), identified by comparison with authentic material.

The major product was the 3 : 5-dinitrobenzoate of the hitherto unknown *epi*calciferol (X). The free hydroxy-compound, with ultraviolet absorption essentially identical with that of calciferol, was obtained by hydrolysis, but it crystallised only after some time, and in view of the relatively small amounts available and also of work in hand to obtain it by another route, its ultimate purification was not attempted. It was characterised additionally as the *p*-nitrobenzoate, and its structure was established by Oppenauer

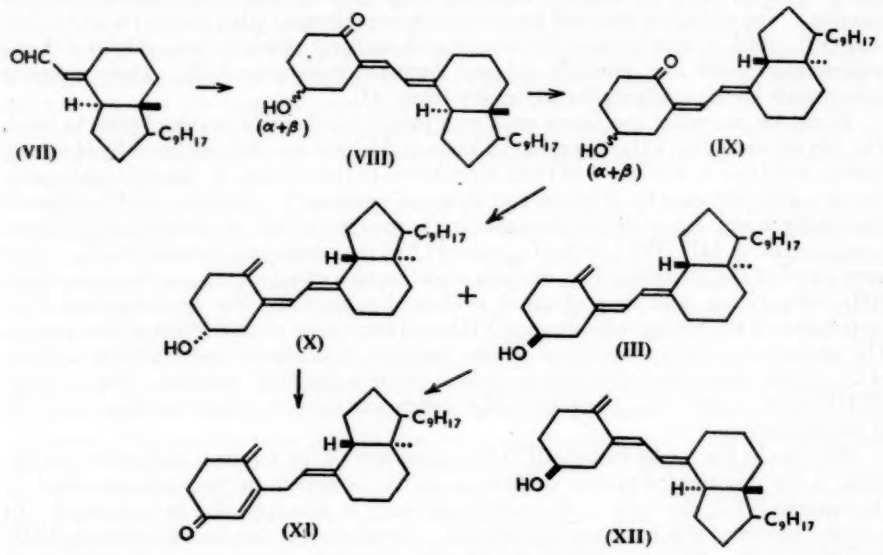
* Steroid nomenclature is used for this and succeeding compounds.

[11] Inhoffen, Quinkert, Hess, and Erdmann, *Chem. Ber.*, 1956, **89**, 2273.
[12] Windaus and Thiele, *Annalen*, 1935, **521**, 160.
[13] Heilbron, Jones, Samant, and Spring, *J.*, 1936, 905.
[14] Windaus and Riemann, *Z. physiol. Chem.*, 1942, **274**, 206.
[15] Inhoffen, Brückner, and Gründel, *Chem. Ber.*, 1954, **87**, 1.

XUM

oxidation to the ketone (XI), characterised as the semicarbazone,[16] which was identical with material similarly obtained from calciferol.

We believe that the above experiments represent the first partial synthesis of calciferol, but, since Inhoffen and his associates [17] have recently claimed to have effected a partial synthesis, their work must now be considered. Koevoet *et al.*[18] had shown that calciferol, like other partly-*cis*-polyenes, is isomerised by iodine to the all-*trans*-isomer, and Inhoffen *et al.*[11] isolated the resulting 5 : 6-*trans*-calciferol (XII), m. p. 99—101°, $[\alpha]_D$ +223° (in $C_6H_6$). Inhoffen, Quinkert, and Hess [17] then showed that this compound was partially




reconverted into calciferol by irradiation. Clearly, if 5 : 6-*trans*-calciferol could be obtained synthetically the combined processes would amount to a partial synthesis of the vitamin. Inhoffen, Kath, Sticherling, and Brückner [4] have reported synthetic work to this end; they acetylated an epimer mixture (VIII), subjected the product to a Wittig reaction, and, after hydrolysis, obtained material which they refer to as "5 : 6-*trans*-vitamin $D_2$" and regard as a mixture of 5 : 6-*trans*-calciferol (XII) and its $C_{(3)}$-epimer. Their synthetic material had m. p. 125—126°, $[\alpha]_D$ +74·8° (in $C_6H_6$); attention is directed to these constants, which are very different from those of the authentic 5 : 6-*trans*-calciferol. The Brunswick workers' claim [17] to a partial synthesis of calciferol appears premature in that an essential link in their synthetic chain is as yet missing. If they are able to isolate authentic 5 : 6-*trans*-calciferol from their synthetic material their work will then constitute a partial synthesis of the vitamin. In view, however, of the ready separation of the 5 : 6-*cis*-epimers in our work, and also of the constants reported for "5 : 6-*trans*-vitamin $D_2$" it seems possible that the latter may be essentially homogeneous, in which case it would presumably correspond, not to 5 : 6-*trans*-calciferol, but to 5 : 6-*trans-epi*-calciferol.

## Experimental

cis-2-2′-cyclo*Hexylidene-ethylidene*cyclo*hexanone* (V).—A solution of the *trans*-isomer [7] (160 mg.) in light petroleum (1 l.; b. p. 40—60°) contained under nitrogen in a quartz flask was

[16] Windaus and Buchholz, *Z. physiol. Chem.*, 1938, **256**, 273; Trippett, *J.*, 1955, 370.
[17] Inhoffen, Quinkert, and Hess, *Naturwiss.*, 1957, **44**, 11.
[18] Koevoet, Verloop, and Havinga, *Rec. Trav. chim.*, 1955, **74**, 788.

irradiated for 2 hr. with light from a Mazda No. 19 mercury-vapour lamp; the extinction measured at 309 mμ had then decreased by 17%. The solution was concentrated under reduced pressure and passed through a column of neutral alumina (Woelm; Grade II) containing 1% of fluorescent zinc oxide [19] (Leuchtfarbe K4 Grün 1, from Dr. W. Franke, Frankfurt-am-Main; we are most grateful to Dr. Franke for a sample of this material). The chromatogram was developed first with light petroleum (b. p. 60—80°) and then with the same solvent mixed with benzene (10% v/v); examination under ultraviolet light (365 mμ) then revealed two distinct zones, and as the development continued the corresponding eluates were collected separately. Evaporation of the eluate which emerged first, and crystallisation from ethanol at −40° gave the cis-*dienone* (50 mg.), m. p. 33—33·5° (mixed m. p. with the *trans*-isomer, 28—31°) (Found: C, 82·4; H, 9·85. $C_{14}H_{20}O$ requires C, 82·3; H, 9·9%). The *semicarbazone* (Found: C, 69·1; H, 9·05. $C_{15}H_{23}ON_3$ requires C, 68·9; H, 8·9%) had m. p. 175° (rapid heating); it then resolidified and remelted at 194—195°; the semicarbazone of the *trans*-isomer has m. p. 196—197°. A mixture of the semicarbazones of the *cis*- and *trans*-dienones had m. p. 157—160° (rapid heating).

Evaporation of the second eluate from the chromatogram, and crystallisation from ethanol at 0° gave the *trans*-dienone, m. p. 67°.

For preparative work an irradiation vessel constructed from two large Pyrex beakers was used. The larger outer beaker was cooled in a bath; in the inner, smaller beaker was placed the lamp, and the space between the beakers contained the solution of *trans*-dienone, which was stirred with a current of nitrogen. A typical solution of the dienone (400 mg.) in methanol (1300 c.c.) after irradiation for 1 hr. at room temperature (ice-bath) was irradiated for a further 2 hr. at −60° (−80° bath), the extinction at 309 mμ falling by 32%. The product was isolated by dilution with water and extraction with ether–light petroleum (b. p. 40—60°) (1 : 1) and chromatographed rapidly on a wide column (diam., 3·5 cm.) of alumina (75 g.; Grade II neutral), development being with light petroleum (b. p. 60—80°) containing 15% (v/v) benzene. Delay at this stage leads to isomerisation. Evaporation of the first eluate gave an oil (305 mg.) which on crystallisation as before gave the *cis*-dienone (230 mg.), m. p. 33°.

cis-1-2′-cyclo*Hexylidene*-*ethylidene*-2-*methylene*cyclo*hexane* (II).—1·0N-Ethereal butyllithium (1 equiv.) was added under nitrogen to a stirred suspension of methyltriphenylphosphonium bromide (1 g.) in dry tetrahydrofuran (30 c.c.). Stirring was continued for 30 min., after which a solution of the *cis*-dienone (V) (300 mg.) in tetrahydrofuran (1 c.c.) was added; after a further 5 min. a few drops of acetone were added to destroy the excess of phosphorane; the mixture was then kept at room temperature for 7 hr. and evaporated under reduced pressure. The residue was distributed between 50% aqueous methanol (20 c.c.) and light petroleum (75 c.c.; b. p. 40—60°), and the aqueous phase again extracted with light petroleum. The combined petroleum phases were washed with 50% aqueous methanol and with water, dried, and filtered through neutral alumina (2 g.; Grade II). The filtrate was evaporated and the residue distilled rapidly (important) at 75° (bath temp.)/$6 \times 10^{-4}$ mm., to give the cis-*triene* (250 mg.) as a colourless mobile oil (Found: C, 88·55; H, 10·8. $C_{15}H_{22}$ requires C, 89·0; H, 11·0%). Microhydrogenation in alcohol with palladium charcoal required 3·06 mols. of hydrogen. When the triene had been kept under nitrogen at 80° for 4 hr. it showed $\lambda_{max.}$ 240 mμ (ε 12,300 in EtOH); the original $\nu_{max.}$ 891 cm.$^{-1}$ (=$CH_2$) had disappeared and a new $\nu_{max.}$ 1380 cm.$^{-1}$ (–$CH_3$) had appeared.

*Reaction of the* cis-*Triene* (II) *with Maleic Anhydride*.—A solution of the *cis*-triene (135 mg.) and maleic anhydride (80 mg.) in benzene (4 c.c.) was heated under reflux for 6½ hr. The benzene was removed and the residue saponified with 6% aqueous potassium hydroxide (5 c.c.) at 100° for 45 min. The cooled and diluted solution was extracted with chloroform, the extract discarded, and the aqueous phase acidified and re-extracted. Evaporation of the extract and crystallisation from aqueous alcohol gave the dibasic *acid* (VI) (65 mg.) as a hydrate, prisms, m. p. 103° (decomp.), which could not be completely dehydrated. Anhydrous material, m. p. 179—182° (decomp.), was obtained by crystallisation from tetrahydrofuran–light petroleum (b. p. 40—60°) followed by drying at 100°/10 mm. (Found: C, 71·6; H, 8·25. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·2%). The isomeric dibasic acid [3] from the *trans*-triene (I) has m. p. 178—182° (decomp.); a mixture of the two had m. p. 165—170° (decomp.).

*Preparation of the* $C_{27}$ trans-*Dienone Epimers* (VIII).—Solutions of 4-acetoxy*cyclo*hexanone (6 g.) and the $C_{21}$ αβ-unsaturated aldehyde (VII) (1 g.) in ethanol (20 c.c.) and sodium ethoxide

[19] Brockmann and Beyer, *Angew. Chem.*, 1951, **63**, 133.

(140 mg. of sodium) in ethanol (20 c.c.) were cooled to −20° and mixed, and the mixture kept at −20° for 2¼ hr., then at 0° for 5 min., and next acidified with acetic acid (0·5 c.c.) in alcohol (5 c.c.). The solution was diluted with aqueous sodium hydrogen carbonate, and the product isolated with ether and dried by distillation with benzene under reduced pressure. It was adsorbed on neutral alumina (140 g.; Grade III) containing 1% of fluorescent zinc oxide, the progress of the chromatogram being observed by examination under light of 365 mμ. Development with light petroleum (b. p. 60—80°) containing 10% (v/v) of benzene removed a light-absorbing band which contained an oil (250 mg.) whose absorption indicated that it was the acetate of the required dienone. Development with benzene alone and then with benzene containing 6% of ether removed several small light-absorbing bands; development with benzene containing 25% of ether then eluted the main light-absorbing zone; the corresponding filtrate was collected in two fractions. That which emerged first was evaporated and the residue crystallised from light petroleum (b. p. 60—80°), providing the required epimer mixture (260 mg.) as blades, m. p. 144—145°, $[\alpha]_D^{20}$ +165° (*c* 1·4 in $C_6H_6$) (Found: C, 80·95; H, 10·4. Calc. for $C_{37}H_{48}O_3$: C, 81·3; H, 10·6%). We regret that the rotation was incorrectly recorded earlier [1] owing to an arithmetical error. The filtrate from the second part of the main light-absorbing zone of the chromatogram provided needles (55 mg.), m. p. 135°, $[\alpha]_D^{20}$ +120° (*c* 1·6 in $C_6H_6$), which were not further examined.

*Reaction of Methylenetriphenylphosphorane and the Epimeric* cis-*Dienones* (IX).—The above *trans*-dienone epimer mixture, $[\alpha]_D^{20}$ +165° (395 mg.), dissolved in methanol (2 l.), was irradiated at −65° for 2 hr., change in the extinction at 310 mμ having become very slow. The *cis*-dienone epimer mixture (385 mg.), $[\alpha]_D^{20}$ +55° (*c* 1·2 in $C_6H_6$), was isolated by dilution with water and extraction with ether and benzene; it did not crystallise. Its solution in tetrahydrofuran (5 c.c.) was added to a stirred solution of the phosphorane prepared under nitrogen from methyltriphenylphosphonium bromide (1·15 g.), suspended in tetrahydrofuran (20 c.c.), and 1·1N-ethereal butyl-lithium (2·9 c.c.). After 25 min. excess of phosphorane was destroyed with acetone, the solution was kept at room temperature for 7 hr., then treated with water (0·5 c.c.), and the solvents were removed under reduced pressure. The residue was distributed between light petroleum (100 c.c.; b. p. 40—60°) and 30% aqueous methanol (30 c.c.). The petroleum phase, after being washed with 50% aqueous methanol and then with water, was dried and evaporated under reduced pressure, giving an oil (525 mg.), $\lambda_{max.}$ 265—266 mμ ($E_{1\,cm.}^{1\%}$ 256 in EtOH); these values were not changed after treatment with dilute hydrochloric acid. The oil, dissolved in light petroleum (b. p. 40—60°), was chromatographed on neutral alumina (25 g.; Grade III), development being with light petroleum (b. p. 60—80°), then benzene (150 c.c.), and finally benzene–ether (10 : 1, 250 c.c.). The desired product was present in the benzene eluate, evaporation of which gave an oil (310 mg.), $\lambda_{max.}$ 265—266 mμ ($E_{1\,cm.}^{1\%}$ 395); rechromatographed on alumina this gave material (200 mg.), $E_{1\,cm.}^{1\%}$ 432. It was kept overnight at room temperature with 3 : 5-dinitrobenzoyl chloride (400 mg.) and pyridine (5 c.c.), and the mixture worked up in the usual way.

Crystallisation from acetone–alcohol gave a first crop (139 mg.) of crystals which were recrystallised from the same solvent, giving epi*calciferyl* 3 : 5-*dinitrobenzoate* as fine yellow needles m. p. 148—148·5°, $[\alpha]_D^{20}$ +35° (*c* 1·2 in $C_6H_6$) (Found: C, 71·2; H, 7·85; N, 4·9. $C_{35}H_{46}O_6N_2$ requires C, 71·1; H, 7·85; N, 4·7%). A mixture of this material and authentic calciferyl 3 : 5-dinitrobenzoate had m. p. 136—140°.

The mother-liquors when kept deposited a second crop (41 mg.) of crystals which, after recrystallisation from acetone–alcohol, afforded yellow prisms of calciferyl 3 : 5-dinitrobenzoate, m. p. 148—148·5°, $[\alpha]_D^{20}$ +56° (*c* 1·8 in $C_6H_6$) (Found: C, 71·05; H, 7·85%). It showed no depression on admixture with authentic calciferyl 3 : 5-dinitrobenzoate of m. p. 148—148·5°; Windaus *et al.*[20] record for this compound m. p. 148—149°, $[\alpha]_D^{20}$ +55° (in $C_6H_6$). For hydrolysis, the synthetic material (29 mg.) was dissolved in tetrahydrofuran (2 c.c.) and alcohol (5 c.c.), and the solution treated with potassium hydroxide (0·5 g.) in the minimum volume of water. The mixture was kept overnight, then diluted with water, and the product isolated with light petroleum (b. p. 40—60°). It crystallised from acetone at −15°, giving calciferol (14 mg.), m. p. and mixed m. p. 114—115°, $\lambda_{max.}$ 265—266 mμ (ε 18,300 in EtOH). The infrared spectra of synthetic and authentic specimens (KBr discs) were identical.

epi*Calciferyl* p-*Nitrobenzoate*.—The 3 : 5-dinitrobenzoate (100 mg.) was hydrolysed as described for the calciferyl ester, and gave a gum which when kept without solvent for some

[20] Windaus, Linsert, Lüttringhaus, and Weidlich, *Annalen*, 1932, **492**, 226.

weeks crystallised; the gum had $[\alpha]_D^{19}$ +25° (*c* 2·9 in $C_6H_6$), $\lambda_{max.}$ 265—266 mμ (ε 17,500 in EtOH). A portion was converted in the usual way into the p-*nitrobenzoate*, needles (from acetone–alcohol), m. p. 122—123° (Found: C, 77·1; H, 8·45. $C_{35}H_{47}O_4N$ requires C, 77·0; H, 8·7%).

*Oppenauer Oxidation of* epi*Calciferol.*—A portion (13 mg.) of the above crude *epi*calciferol was oxidised as recorded for calciferol,[16] and the product isolated as the semicarbazone (8 mg.). After crystallisation from alcohol it had m. p. 209—211° (decomp.) (undepressed on admixture with authentic material of the same m. p. prepared from calciferol), and $[\alpha]_D^{20}$ +25° (*c* 0·8 in $CHCl_3$). Inhoffen *et al.*[4] give for this semicarbazone, m. p. 209°, $[\alpha]_D$ +24° (in $CHCl_3$).

We are indebted to the Department of Scientific and Industrial Research for a Maintenance Grant (to I. T. H), and we also acknowledge most gratefully gifts of calciferol from Dr. B. A. Hems of Glaxo Laboratories Limited.

Department of Organic Chemistry,
The University, Leeds, 2.

[*Received, October 16th*, 1957.]

---

## 163. *Calciferol and its Relatives. Part IV.* A Non-photochemical Synthesis of a Model* cis-*Triene.*

By I. T. Harrison and B. Lythgoe.

The bicyclic αβ-unsaturated lactones (III) and (IV) were studied as possible intermediates for a synthesis of the *cis*-triene (II), a simple model for calciferol.

The γ-lactone (III) was transformed in four steps into the *cis*-dienol (XIV) and thence into the *cis*-dienone (XV). This sequence, in conjunction with the conversion of (XV) into (II) described in the preceding paper, provides a new synthesis of the model *cis*-triene by a non-photochemical route.

The present work continues that of the preceding paper in seeking methods to secure the *cis*-configuration of the central double bond of trienes of the calciferol type. The photochemical method there described provided a rational partial synthesis of calciferol, but one which did not completely satisfy us because a photochemical route (admittedly complex) was already available in the normal preparation from ergosterol. We have therefore investigated an alternative approach to calciferol (I), independent of photochemical reactions. As before, the initial experiments were carried out on model compounds, and we now report a second synthesis of the model *cis*-triene (II), based on the established method[1] of preparing *cis*-ethylenic compounds by ring-opening of cyclic unsaturated intermediates.

The bicyclic αβ-unsaturated lactones (III) and (IV) appeared to be suitable as intermediates for this purpose. They contain one ring of the triene (II) and its attached *cis*-semicyclic double bond, together with functional groups at positions appropriate for construction of the rest of the triene molecule. The γ-lactone (III) is obtained[2] by dehydrating 2-oxo*cyclo*hexylacetic acid, but the δ-lactone (IV) was described only very recently. Belleau[3] has prepared it by a Prins reaction between trioxan and *cyclo*hex-1-enylacetic acid in dioxan containing sulphuric acid. The method by which the lactone (IV) was prepared for the present work differs from Belleau's and will be reported in a separate paper.

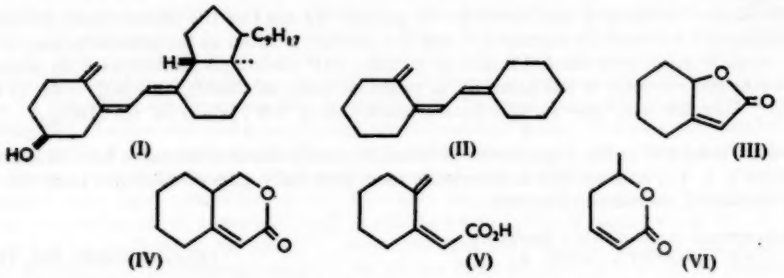
We shall describe first our experiments on the δ-lactone (IV). It is a bicyclic analogue of the lactone[4] (VI), which Linstead and his associates[5] have shown can be converted

* Part III, Harrison and Lythgoe, preceding paper.

[1] For examples, see Crombie, *Quart. Rev.*, 1952, **6**, 101 (p. 135).
[2] Newman and VanderWerf, *J. Amer. Chem. Soc.*, 1945, **67**, 233.
[3] Belleau, *Canad. J. Chem.*, 1957, **35**, 673.
[4] Haynes and Jones, *J.*, 1946, 954.
[5] Eisner, Elvidge, and Linstead, *J.*, 1953, 1373.

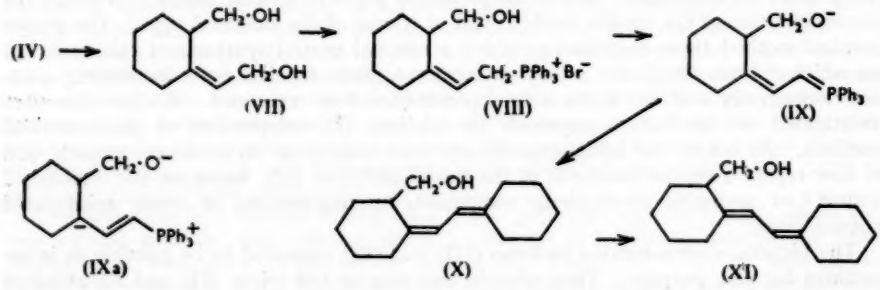
XUM

into hexa-*cis*-2-*trans*-4-dienoic acid by treatment with methanolic sodium methoxide. If the bicyclic lactone reacted in the same way it would give the *cis*-dienoic acid (V) which contains two of the double bonds of the triene (II) and obvious facilities for constructing




the third. However, neither under Linstead's conditions nor under others more vigorous was any conjugated dienoic acid obtained from the bicyclic lactone (IV); the course of the reaction was not determined, but the light absorption of the dienoic acid would have allowed even small amounts to be detected. The high energy of the semicyclic methylene double bond in compound (V) was, of course, expected to make the reaction more difficult than that studied by Linstead. Alternative methods of opening the lactone ring of (IV) were therefore used, as shown below.

The δ-lactone (IV) was reduced with lithium aluminium hydride to the diol (VII), characterised as the di-*p*-nitrobenzoate. The *cis*-geometry was retained during this reduction, as during similar reduction [6] of *cis*-crotonic acid. Next, we wished to replace the allylic hydroxyl group of the diol by a bromine atom, whilst leaving the rest of the molecule unchanged. Reagents permitting a unimolecular replacement mechanism were




expected to cause some geometric inversion, so we chose triphenyl phosphite benzylobromide as the reagent; Landauer and Rydon [7] have shown that the corresponding methiodide converts *neo*pentyl alcohol into the iodide without rearrangement. There is also evidence in Rydon's work that such reagents attack allylic primary alcohols more rapidly than ordinary primary alcohols, which in turn react more rapidly than ordinary secondary alcohols. We found that reaction of the diol (VII) with slightly more than 1 mol. of triphenyl phosphite benzylobromide effected the replacement of the allylic hydroxyl group fairly selectively, and when the crude product was treated with triphenylphosphine it gave the crystalline phosphonium bromide (VIII).

The derived Wittig [8] reagent (IX), obtained by the action of butyl-lithium (1·9 mols.), reacted with *cyclo*hexanone, giving the *cis*-dienol (X) together with a small amount of the

[6] Hatch and Nesbitt, *J. Amer. Chem. Soc.*, 1950, **72**, 727.
[7] Landauer and Rydon, *J.*, 1953, 2224.
[8] Wittig and Schöllkopf, *Chem. Ber.*, 1954, **87**, 1318.

*trans*-isomer (XI). Three features of this reaction deserve mention. First, it will be noted that no protection was necessary for the hydroxyl group of (VIII); the reaction may be compared with that described in Part III, where the unprotected hydroxyl group was present in the ketonic, instead of the phosphorane, component. Secondly, it will be noted that the phosphorane component (IX) is a resonant structure, to which the form (IXa) contributes. In this form the *cis*-double bond has become a single bond; this implies that in the actual molecule the *cis*-double bond has only partial double-bond character, so that its resistance to torsion is less than that of an isolated double bond. It would therefore be expected to undergo geometric inversion relatively easily, and this probably accounts for the production of the *trans*-isomer (XI): in practice it was advisable to generate the reagent (IX), and also to bring it into reaction with *cyclo*hexanone, at low temperatures, as otherwise a larger proportion of the unwanted *trans*-isomer (XI) was obtained. Finally, we have observed that, in Wittig reactions where, as in the present example, a new double bond is formed in conjugation with an existing one, the intermediate zwitterion decomposes readily at room temperature, so that the thermal decomposition frequently used is unnecessary.

The *cis*-dienol (X) was readily freed from the *trans*-isomer (XI) by crystallisation, and then had $\lambda_{max.}$ 242, 250, and 259 mμ (ε 34,300, 38,800, and 27,400 in EtOH). The *trans*-isomer (XI) was best separated as the 3 : 5-dinitrobenzoate, which showed ultraviolet absorption closely similar to those of the *cis*-dienol (X) and its 3 : 5-dinitrobenzoate. This confirms the gross structure of both isomers, since triple maxima at these positions are characteristic [9] of derivatives of di*cyclo*hexylidene-ethane. The *cis*-configuration of the isomer (X) was established by the inversion of its 3 : 5-dinitrobenzoate into that of the *trans*-isomer (XI) in the presence of iodine.

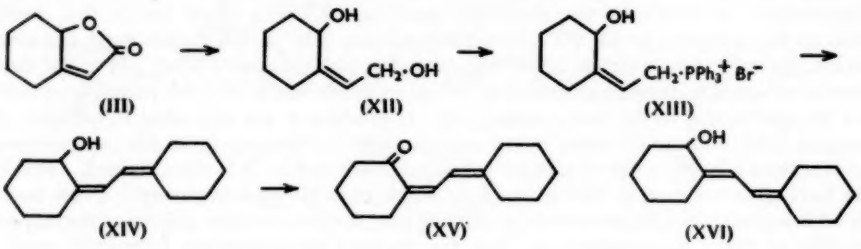
The conversion of *cyclo*hexylmethanol into methylene*cyclo*hexane, formally a dehydration, must be performed indirectly because of the semicyclic nature of the new double bond. Superficially, it appears that the *cis*-dienol (X) could be similarly converted into the desired triene (II), and more readily because of the conjugation present in the triene. We were, however, unable to effect this change. The methods attempted may be summarised as follows. (*a*) *cyclo*Hexylmethyl iodide gives [10] methylene*cyclo*hexane when treated with a base. We were unable to obtain the iodide corresponding to the dienol (X) by treating the dienol with triphenyl phosphite methiodide, or by treating the toluene-*p*-sulphonate with sodium iodide. Direct elimination from the toluene-*p*-sulphonate by reaction with bases was likewise attempted without success; atomic models show that approach to the relevant hydrogen atom is seriously hindered. (*b*) The toluene-*p*-sulphonate of the dienol, unlike that of *cyclo*hexylmethanol, could not be quaternised by treatment with trimethylamine, so that the Hofmann elimination method, by which the *trans*-isomer of the triene (II) has been prepared,[9] was inapplicable here. Displacement reactions at the hydroxymethyl-carbon atom of derivatives of the dienol (X) are, it appears, sterically hindered. (*c*) Pyrolysis [11] of the acetate of the dienol (X) left it unchanged or, under more vigorous conditions, decomposed it completely. (*d*) Whereas benzyl *cyclo*hexylmethyl ether and butyl-lithium give methylene*cyclo*hexane [12] the triene (II) could not be similarly obtained from the benzyl ether of the dienol (X). With the failure of these attempts work on the above route was brought to an end.

We then returned to the bicyclic γ-lactone (III) which we had reduced in earlier experiments to the diol (XII). At that time we were unable to distinguish effectively by selective esterification between the two hydroxyl groups of the diol, but later the need to do so was removed by the finding that triphenyl phosphite benzylobromide was selective

[9] Harrison, Lythgoe, and Trippett, *J.*, 1955, 4016.
[10] Faworski and Borgmann, *Ber.*, 1907, **40**, 4865.
[11] Bailey and King, *J. Amer. Chem. Soc.*, 1955, **77**, 75; Bailey, Hewitt, and King, *ibid.*, p. 357; and later papers by Bailey *et al.*
[12] Method based on the formation of ethylene in similar reactions studied by Wittig and Lohmann, *Annalen*, 1942, **550**, 260; Letsinger and Pollart, *J. Amer. Chem. Soc.*, 1956, **78**, 6079.

XUM

in its action upon alcohols. By using this reagent in the way already described, the diol (XII) was converted into the crystalline phosphonium bromide (XIII), and thence, by a Wittig reaction with *cyclo*hexanone, into the *cis*-dienol (XIV). The gross structure of this dienol was confirmed by its ultraviolet absorption, which is closely similar to that of the




known *trans*-isomer (XVI);[13] since the two compounds were not identical the new dienol had the *cis*-configuration.

On oxidation with manganese dioxide the *cis*-dienol (XIV) was converted into the *cis*-dienone (XV), identical with an authentic specimen prepared by the photoisomerisation described in the preceding paper; additional evidence of the identity was provided by reducing the photochemical sample with sodium borohydride, which gave the *cis*-dienol (XIV) identical with that prepared by the chemical synthesis.

The conversion of the *cis*-dienone (XV) into the *cis*-triene (II) by means of a Wittig reaction was described in the preceding paper, so that the present work constitutes a new synthesis of the model triene by non-photochemical methods. Its extension to a synthesis of one of the vitamins D is under study.

## Experimental

cis-2-(2-*Hydroxymethyl*cyclo*hexylidene*)-*ethanol* (VII).—A solution of the δ-lactone (IV) (55·5 g.) in ether (250 c.c.) was added during 30 min. to a stirred and cooled (−15°) solution of lithium aluminium hydride (13 g.) in ether (500 c.c.); stirring was continued at room temperature for a further 2 hr. Ethyl acetate (50 c.c.) in ether (100 c.c.) was then added, followed by saturated aqueous ammonium chloride (100 c.c.), after which the mixture was filtered and the residue washed with ether. The ether was removed from the united ethereal solutions and the residual viscous oil (55 g.) was dried by distillation with benzene. The p-*nitrobenzoate* separated from alcohol in small crystals, m. p. 131—132° (Found: C, 60·65; H, 5·15. $C_{23}H_{22}O_6N_2$ requires C, 60·8; H, 4·9%).

cis-2-(2-*Hydroxymethyl*cyclo*hexylidene*)-*ethyltriphenylphosphonium Bromide* (VIII).—Triphenyl phosphite benzylobromide was prepared from triphenyl phosphite (119 g.) and benzyl bromide (63 g.) at 170° (sealed tube; 5 hr.). A solution of the reagent in tetrahydrofuran (200 c.c.) was added during 30 min. to a stirred and cooled (0°) solution of the diol (VII) (52·5 g.) in tetrahydrofuran (700 c.c.). A solution of triphenylphosphine (88 g.) in ether (250 c.c.) was then added, and the mixture was kept overnight at room temperature. The crystalline deposit (44·5 g.) was collected, the filtrate was evaporated under reduced pressure, and the residual oil washed with ether (4 × 1 l.), the washings being discarded. Crystallisation of the residue from tetrahydrofuran gave a further crop (33 g.) of crystals. The combined crops were crystallised from hot chloroform by addition of tetrahydrofuran, giving the *phosphonium bromide* (67 g.) as prisms, m. p. 218° (Found: $Br^-$, 16·6. $C_{27}H_{30}OPBr$ requires $Br^-$, 16·6%).

cis-1-2′-cyclo*Hexylidene-ethylidene-2-hydroxymethyl*cyclo*hexane* (X).—The above phosphonium bromide (17 g.) was finely powdered and to its stirred and cooled (−25°) suspension in tetrahydrofuran (700 c.c.) under nitrogen 1·13N-ethereal butyl-lithium (59·5 c.c.) was slowly added. When the solution had become homogeneous, *cyclo*hexanone (10 c.c.) was added, and the solution was allowed to warm to 5°; the deep red colour then faded to orange. The solution was kept overnight at room temperature, the solvents were removed under reduced pressure,

[13] Dimroth and Jonsson, *Ber.*, 1938, **71**, 2658.

and the residue was shaken with light petroleum (250 c.c.; b. p. 40—60°) to induce crystallisation of the triphenylphosphine oxide, which was then removed. The filtrate was shaken with 66% aqueous ethanol, and the light petroleum phase evaporated, finally at 40°/0·2 mm. in order to remove any *cyclo*hexanone. The product (11 g.) was spectrophotometrically 60% pure; it was chromatographed on neutral alumina (250 g., grade III). Development with light petroleum (1 l.; b. p. 40—60°) gave a fraction (7·0 g.; 63% pure); continued development with light petroleum (1 l.; b. p. 60—80°) gave a further fraction (0·76 g.; 90% pure); development with benzene (500 c.c.) gave a further fraction (1·25 g.; 74% pure). Rechromatography of the first and the third fraction gave 4·16 g. of material *ca.* 85% pure; it was combined with the second fraction and crystallised from aqueous methanol, giving needles (3·3 g.), m. p. 68·5°. Recrystallisation from light petroleum, b. p. 40—60°, gave the pure cis-*dienol*, m. p. 70° (Found: C, 81·55; H, 10·85. $C_{15}H_{24}O$ requires C, 81·75; H, 11·0%). The 3 : 5-*dinitrobenzoate* separated from light petroleum (b. p. 60—80°) as yellow needles, m. p. 126° (Found: C, 63·85; H, 6·45; N, 7·0. $C_{22}H_{26}O_6N_2$ requires C, 63·7; H, 6·3; N, 6·8%), and had $\lambda_{max.}$ 240·5, 249, and 258 mμ (ε 43,100, 42,400, and 28,300 in EtOH).

When a portion of the above dienol of purity *ca.* 85% (*i.e.*, before crystallisation) was esterified with 3 : 5-dinitrobenzoyl chloride in pyridine it furnished a product which was separated by crystallisation into the more soluble 3 : 5-dinitrobenzoate of the above *cis*-dienol (81%) and the less soluble 3 : 5-*dinitrobenzoate* of the isomeric *trans*-dienol (4%), compact yellow needle aggregates (from alcohol), m. p. 144°, depressed to 106—110° on admixture with the *cis*-isomer (Found: C, 63·4; H, 6·45%). This had $\lambda_{max.}$ 240·5, 249, and 258 mμ (ε 44,100, 44,200, and 29,200 in EtOH). When the above dienol was prepared by a Wittig reaction at *ca.* 40°, its composition, determined by the 3 : 5-dinitrobenzoate method, was *cis*- : *trans*-dienol = 4 : 1.

A solution of the 3 : 5-dinitrobenzoate of the *cis*-dienol (30 mg.) in light petroleum (30 c.c.) containing iodine (2 mg.) was heated under reflux for 10 hr. and the product crystallised from alcohol; this gave (*a*) the ester of the *trans*-dienol (12 mg.), m. p. and mixed m. p. 143°, and (*b*) unchanged *cis*-material (8 mg.), m. p. 126°.

*Methylene*cyclo*hexane from Benzyl*cyclo*hexylmethyl Ether* (with A. Masood).—The benzyl ether (5·1 g.) and 0·76N-ethereal butyl-lithium (37 c.c.) were kept at room temperature for 10 hr., and the solution was diluted with ether, washed with water, dried, and distilled through a Vigreux column. The first portion of the ether distillate was rejected; the later fraction, collected from 70° to 90°, contained ether and methylene*cyclo*hexane, identified as the nitrosopiperidide, m. p. 126—127° (Found: C, 68·7; H, 10·5. Calc. for $C_{12}H_{22}ON_2$: C, 68·5; H, 10·5%). The yield of the hydrocarbon, determined by titration with bromine, was 60%.

cis-2-(2-*Hydroxy*cyclo*hexylidene*)-*ethanol* (XII).—Reduction of the γ-lactone (III) (15 g.) by lithium aluminium hydride as described for the δ-lactone (IV) gave the crude diol (15 g.), b. p. 117—120°/6 × $10^{-4}$ mm. The *di*-p-*nitrobenzoate* separated from ethyl acetate as pale yellow needles, m. p. 132° (Found: C, 60·25; H, 4·6; N, 6·55. $C_{22}H_{20}O_8N_2$ requires C, 60·0; H, 4·5; N, 6·4%).

cis-2-(2-*Hydroxy*cyclo*hexylidene*)-*ethyltriphenylphosphonium Bromide* (XIII).—Triphenyl phosphite (15·4 g.) and benzyl bromide (8·1 g.) were kept together at 120° with exclusion of moisture for 48 hr. The cooled product crystallised from tetrahydrofuran (40 c.c.), giving triphenyl phosphite benzylobromide (19 g.) as very hygroscopic prisms, m. p. 160°. A portion (15 g.) was melted in a vacuum and then dissolved whilst still warm in tetrahydrofuran (20 c.c.); the solution was added to a stirred and cooled (cold water) solution of the diol (XII) (6 g.) and triphenylphosphine (8·2 g.) in tetrahydrofuran (40 c.c.). The mixture was kept overnight, the tetrahydrofuran removed under reduced pressure, and the syrupy residue washed several times with ether, the washings being discarded. Crystallisation of the residue from tetrahydrofuran and then from alcohol–tetrahydrofuran gave the phosphonium bromide (4·02 g.) as colourless prisms, m. p. *ca.* 102—108° (gas evolution). This material was an ethanol solvate which could not be completely desolvated without decomposition. Crystallisation from water gave the *monohydrate*, m. p. 110—116° (decomp.) (Found: $Br^-$, 16·3. $C_{26}H_{28}OPBr,H_2O$ requires $Br^-$, 16·5%). This material also decomposed when complete dehydration was attempted.

cis-2-2′-cyclo*Hexylidene-ethylidene*cyclo*hexanol* (XIV).—(*a*) The above ethanol solvate (2·32 g.) was finely powdered and suspended in tetrahydrofuran (40 c.c.), and to the stirred suspension under nitrogen at −65° was added during 5 min. ethereal butyl-lithium (3 mols.). After the addition of *cyclo*hexanone (3 c.c.) the solution was allowed to attain room temperature, then kept for 18 hr. Water (5 c.c.) was added, the solvents were removed under strongly

reduced pressure, and the residue was distributed in the usual manner between 50% methanol (50 c.c.) and benzene (50 c.c.). The contents of the benzene layer were chromatographed on neutral alumina (100 g.; Grade II), development being first with light petroleum (b. p. 40—60°) and later with benzene. One fraction of the benzene eluate provided an oil (0·41 g.) which crystallised from light petroleum (b. p. 40—60°), giving the cis-*dienol* (251 mg.), as needles m. p. 110—111° (Found: C, 81·5; H, 10·55. $C_{14}H_{22}O$ requires C, 81·6; H, 10·8%), $\lambda_{max.}$ 240, 247, and 256 mμ (ε 30,300, 35,200, and 23,600 in EtOH). The isomeric *trans*-dienol has m. p. 125—126° (cf. ref. 13).

(*b*) *cis*-2-2′-*cyclo*Hexylidene-ethylidene*cyclo*hexanone (230 mg.), prepared by the photo-isomerisation described in Part III, was reduced in methanol (7 c.c.) and water (0·3 c.c.) by gradual addition of sodium borohydride. Dilution with water, isolation with ether, and crystallisation from light petroleum (b. p. 60—80°) gave the *cis*-dienol (210 mg.), m. p. 110—111°, undepressed on admixture with material obtained by method (*a*).

cis-2-2′-cyclo*Hexylidene-ethylidene*cyclo*hexanone* (XV).—The *cis*-dienol (100 mg.), prepared by method (*a*), was dissolved in ether (150 c.c.) and shaken with manganese dioxide (13 g. added in small portions) during 5 hr. The solution was filtered, the residue was washed thoroughly with ether, and the filtrate and washings were combined and evaporated under reduced pressure. Crystallisation of the residue from alcohol at −40° gave the *cis*-dienone (21 mg.), m. p. 32—32·5°, undepressed on admixture with material prepared as described in Part III; it had $\lambda_{max.}$ 304—305 mμ (ε 15,000 in EtOH).

We gratefully acknowledge a grant from Imperial Chemical Industries Limited. One of us (I. T. H.) thanks the Department of Scientific and Industrial Research for a Maintenance Award.

Department of Organic Chemistry,
The University, Leeds, 2.

[*Received, October 16th*, 1957.]

---

## 164. *Studies in Co-ordination Chemistry. Part III.* The Thermodynamics of Interaction between Heterocyclic Bases and (Diacetyl Bisbenzoylhydrazone)nickel(II) in Benzene.*

By L. Sacconi, G. Lombardo, and P. Paoletti.

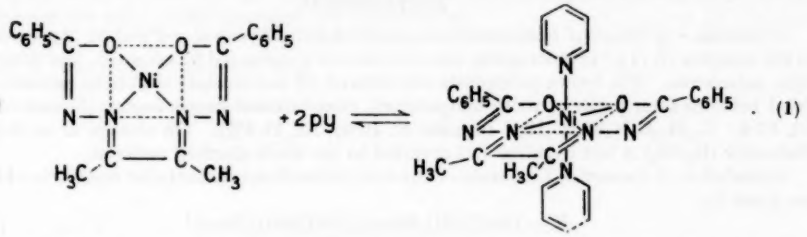
The planar complex (diacetyl bisbenzoylhydrazone)nickel(II) is diamagnetic, with $dsp^2$ hybridisation, and forms addition compounds with various nitrogen bases containing two molecules of base. The different absorption characteristics of the two co-ordination compounds allow the formation constants of the complexes in non-polar solvents to be determined by spectrophotometry. The main factors controlling the stability of the complexes have been investigated and the relationship between the base strength and co-ordinating tendency toward (diacetyl bisbenzoylhydrazone)nickel(II) is discussed in terms of electronic and steric factors. From the measurements of the temperature dependence of the formation constants we calculated the heats of reaction and free-energy and entropy changes; these are discussed. The different orders of entropy change observed can be explained as a particular type of "*ortho*-effect" and by the π-bond character ascribed to the co-ordinate links between nickel and the nitrogen atom of the heterocyclic amines.

The number of thermodynamic data, *e.g.*, heats and entropies of reaction, for complex equilibria is very small.[1] Most investigations have been carried out in aqueous solution and so refer to displacement reactions, *i.e.*, water for another ligand. Since the thermodynamic data relative to such hydration processes cannot be determined unequivocally, the results are generally uncertain.

* Part II, Sacconi, Paoletti, and Maggio, *J. Amer. Chem. Soc.*, 1957, **79**, 4067.

[1] Rasmussen, *Acta Chem. Scand.*, 1956, **10**, 1279.

The study of the equilibria between (diacetyl bisbenzoylhydrazone)nickel(II) (I) and a series of bases, in a " non-co-ordinating " solvent, is free from these limitations: the reactants are uncharged and anhydrous, and no displacement of ligands occurs during the




reaction, which consists solely in the addition of two molecules of base to the square planar nickel complex. Owing to the nature of the metal atom and the peculiar steric requirements of the reference complex molecule, these equilibria are valuable for study of the structure of the bases and the bond types involved.

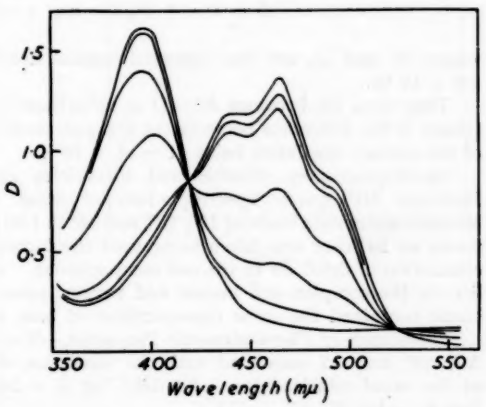



FIG. 1. *Absorption curves of (diacetyl bisbenzoylhydrazone)nickel(II) in benzene and benzene–pyridine solutions.*

(Diacetyl bisbenzoylhydrazone)nickel(II), [Ni(DBH)], (I), described previously,[2] is diamagnetic and a square planar structure with $dsp^2$ hybridation has been suggested. It gives green diamagnetic solutions in " non-co-ordinating " solvents, *e.g.*, chloroform and benzene, and the solutions in donor solvents are yellow-brown and paramagnetic (*e.g.*, in pyridine $\mu_{eff.} = 3{\cdot}2$ B.M.). This can be attributed to the formation of an octahedral complex (II) according to (1).

In fact a pyridine adduct can easily be prepared by carrying out reaction (1) in chloroform. It is paramagnetic ($\mu_{eff.} = 2{\cdot}5$ B.M.) and presumably octahedral with $d^2sp^3$ hybridisation, with the pyridine molecules in the *trans*-position. Low magnetic susceptibilities have frequently been observed in similar adducts.[3]

Equilibrium (1) can be studied spectrophotometrically because the complex (I) and its pyridine adduct absorb at different wavelengths with absorption maxima at 392 mμ (in benzene) and 466 mμ (in 0·15M-pyridine solution in benzene) respectively. These absorption curves, and those of intermediate composition, form a family with an isosbestic point at their intersection, 421 mμ (Fig. 1), indicating the presence of only two

[2] Sacconi, *Z. anorg. Chem.*, 1954, **275**, 249.
[3] Cf. Basolo and Matoush, *J. Amer. Chem. Soc.*, 1953, **75**, 5663; Draney and Cefola, *ibid.*, 1954, **76**, 1975.

XUM

complex species in solution. Similar graphs with sharp isosbestic points are obtained for all the bases employed.

## Experimental

*Preparation of (Diacetyl Bisbenzoylhydrazone)nickel*(II),*2Pyridine.*—Pyridine (2 g.) was added to the complex (I) (1 g.) in chloroform, and the solution evaporated to a few c.c., and diluted with light petroleum. The brown precipitate was filtered off and washed with light petroleum, and, dried between filter paper at room temperature, gave brilliant brown *leaflets* (Found: N, 16·6; Ni, 17·4. $C_{18}H_{16}O_2N_4Ni,2C_5H_5N$ requires N, 16·6; Ni, 17·4%). On storage in an evacuated desiccator ($H_2SO_4$) it lost pyridine and reverted to the black starting material.

*Calculation of Formation Constants.*—The total formation constants for equilibria of type (1) are given by

$$K = [\text{Ni(DBH)},2\text{Base}]/[\text{Ni(DBH)}][\text{Base}]^2 \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Solutions of the nickel complex (I) in benzene and pyridine–benzene obey Beer's law and its concentration and that of its adduct with two molecules of base can be obtained directly by spectrophotometry. If $\alpha$ is the fraction of " free " complex and $D$ the observed optical density at a given wavelength, then, as $c$ and $l$ are kept constant ($c = 1 \times 10^{-4}$),

$$D = D_1\alpha + D_2(1 - \alpha); \quad \alpha = (D - D_2)/(D_1 - D_2)$$

where $D_1$ and $D_2$ are the observed optical densities of Ni(DBH) and Ni(DBH),2Base at $1{\cdot}0 \times 10^{-4}$M.

Then eqn. (2) becomes $K = (1 - \alpha)/(\alpha[\text{Base}]^2)$. The concentration of the " free " base, [Base], is the difference between the concentration of base added and twice the concentration of the adduct, the latter being $(1 - \alpha) \times 10^{-4}$.

*Spectrophotometry.*—Visible and ultraviolet absorption spectra were measured with a Beckman DU quartz spectrophotometer fitted with a thermostated cell compartment.[4] Measurements were made at 10°, 25°, and 45° in 1·00 cm. stoppered silica cells. During measurements at 10° care was taken to prevent the formation of a film of moisture on the cells by circulation of dried air in the cell compartment. The solutions used contained $10^{-4}$ mole per litre of the complex and known and varying amounts of each base. The solution used as a blank contained the same concentration of base as the sample.

*Calculation of Thermodynamic Properties.*—The standard molar thermodynamic quantities $\Delta G$, $\Delta H$, and $\Delta S$ associated with the formation of the complexes were calculated by means of the usual relationships $-2{\cdot}303RT \log K = \Delta G = \Delta H - T\Delta S$ and $\Delta H = 2{\cdot}303RT_1T_2 \times (\log K_2 - \log K_1)/(T_2 - T_1)$.

$\Delta H$ is constant within the experimental error over the range of temperatures investigated as shown by the linear plot of log $K$ against $1/T$ in Fig. 2.

*Magnetic Measurements.*—The magnetic susceptibility of (diacetyl bisbenzoylhydrazone)-nickel(II) in pyridine was determined by the Gouy method.[5] The susceptibilities of the solid and the solid pyridine adduct were measured by means of the interferometric Bhatnagar balance [6] with the Faraday method. The molar susceptibility of the addition compound was calculated by using an effective molecular weight derived from the actual concentration of pyridine present in the compound. Diamagnetic corrections were calculated from Pascal's constants.

*Materials.*—Benzene was carefully purified by standard methods.[7] The amines, which were good-quality commercial products (Fluka), were purified until their physical constants agreed closely with the values in the literature. Usually they were refluxed for several hours over potassium hydroxide or barium oxide, fractionated through a column of 40 theoretical plates packed with Fenske glass helices, and the constant-boiling middle fractions collected.

*Results.*—The equilibrium constants for reactions of type (1) at 10°, 25°, and 45° are in Table 1. $K_H$ is the value of the acid dissociation constants of the amines and $K_{Ag}$ some of the

[4] Bell and Stryker, *Science*, 1947, **105**, 415.
[5] Sacconi, Paoletti, and Del Re, *J. Amer. Chem. Soc.*, 1957, **79**, 4062.
[6] Sacconi, *ibid.*, 1954, **76**, 3400.
[7] Weissberger, " Organic Solvents," Interscience Publishers, Inc., New York, 1955.

corresponding formation constants with silver(I) from the literature. $R = \log K/pK_H$ and $R' = \log K_{Ag}/pK_H$. $Q_N$ is the calculated charge density on the nitrogen atom.

In Fig. 3 $\log K$ is plotted against $pK_H$ for the bases. The precision of the values was $\pm 0.02$ for $\log K$, $\pm 0.02$ kcal. mole$^{-1}$ for $\Delta G$ and $\Delta H$ ($\pm 0.3$ kcal. mole$^{-1}$ for quinoline and *iso*quinoline), and $\pm 0.1$ e.u. for $\Delta S$ ($\pm 1$ for quinoline and *iso*quinoline).

FIG. 2. *Plot of* $\log K$ *against* $1/T$ (*for numerals, see Tables*).

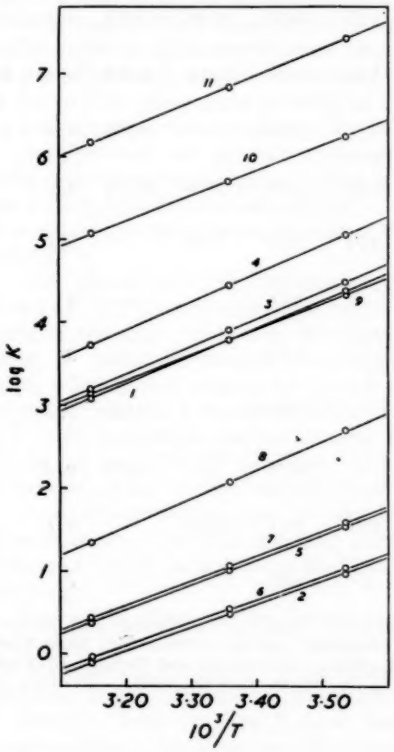
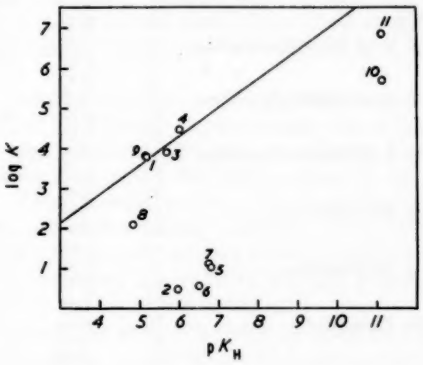



FIG. 3. *Plot of* $\log K$ *against* $pK_H$ (*for numerals, see Tables*).




## DISCUSSION

The values of $\log K$ for pyridine and substituted pyridines fall into two main groups: the first includes pyridine and 3-, 4-, and 3 : 4-substituted pyridines with values of $R$ ranging from 0·69 to 0·74. The values of $\log K$ for such bases on the plot in Fig. 3 lie roughly on one straight line of slope equal to the mean values of $R$. The second group includes the 2-methylpyridines, *i.e.*, 2-methyl- and 2 : 4-, 2 : 5-, 2 : 6-dimethyl-pyridine. Their values of $\log K$ are more than 3·5 logarithmic units lower than those of the first group and the values of $R$ range from 0·08 to 0·15. The values of $\log K$ for the quinoline and for the secondary amines piperidine and pyrrolidine lie apart from these two groups.

The electron density $Q_N$ at the nitrogen atoms of the heterocyclic bases depends on the environment of the nitrogen atom through operation of the inductive and mesomeric effect of the substituent. In the picolines and lutidines the inductive ($+I$) and the hyperconjugative effect of the methyl group increase the charge density on the nitrogen atom.[8] Values of $Q_N$ and $pK_H$ (Table 1) show that the base strengths of pyridine, the picolines,

[8] Cf. H. C Brown and Barbaras, *J. Amer. Chem. Soc.*, 1947, **69**, 1137.

and *iso*quinoline run parallel to the charge densities on nitrogen atoms. The values of log $K$ now observed for all these bases except 2-picoline also run parallel to the charge densities on the nitrogen atom. This suggests that the availability of electrons on the

TABLE 1. *Formation constants of (diacetyl bisbenzoylhydrazone)nickel(II) with heterocyclic bases, and related data.*

| No. | | $t$ (°C) | log $K$ | p$K_{II}$ | log $K_{Ag}$ | $R$ | $R'$ | $Q_N$ | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Pyridine | 10 | 4·36 | | | | | | |
| | | 25 | 3·78 | 5·23 | 4·22 | 0·72 | 0·81 | 1·274 | *a, b, c, d* |
| | | 45 | 3·09 | | | | | | |
| 2 | 2-Methylpyridine | 10 | 0·98 | | | | | | |
| | | 25 | 0·48 | 5·97 | 4·68 | 0·08 | 0·78 | 1·494 | *a, b, c, d* |
| | | 45 | −0·11 | | | | | | |
| 3 | 3-Methylpyridine | 10 | 4·49 | | | | | | |
| | | 25 | 3·90 | 5·68 | — | 0·69 | — | 1·368 | *a, d* |
| | | 45 | 3·20 | | | | | | |
| 4 | 4-Methylpyridine | 10 | 5·06 | | | | | | |
| | | 25 | 4·45 | 6·02 | 4·70 | 0·74 | 0·78 | 1·521 | *a, c, d* |
| | | 45 | 3·73 | | | | | | |
| 5 | 2 : 4-Dimethylpyridine | 10 | 1·55 | | | | | | |
| | | 25 | 1·02 | 6·79 | 5·18 | 0·15 | 0·76 | — | *a, c* |
| | | 45 | 0·39 | | | | | | |
| 6 | 2 : 5-Dimethylpyridine | 10 | 1·03 | | | | | | |
| | | 25 | 0·54 | 6·51 | — | 0·08 | — | — | *a* |
| | | 45 | −0·04 | | | | | | |
| 7 | 2 : 6-Dimethylpyridine | 10 | 1·58 | | | | | | |
| | | 25 | 1·05 | 6·75 | — | 0·15 | — | — | *a* |
| | | 45 | 0·42 | | | | | | |
| 8 | Quinoline | 10 | 2·68 | | | | | | |
| | | 25 | 2·08 | 4·85 | — | 0·43 * | — | 1·326 | *a, d* |
| | | 45 | 1·34 | | | | | | |
| 9 | *iso*Quinoline | 10 | 4·34 | | | | | | |
| | | 25 | 3·78 | 5·14 | — | 0·73 * | — | 1·278 | *a, d* |
| | | 45 | 3·14 | | | | | | |
| 10 | Piperidine | 10 | 6·24 | | | | | | |
| | | 25 | 5·70 | 11·13 | 6·48 | 0·51 | 0·58 | — | *a, c* |
| | | 45 | 5·06 | | | | | | |
| 11 | Pyrrolidine | 10 | 7·42 | | | | | | |
| | | 25 | 6·84 | 11·11 | — | 0·61 | — | — | *e* |
| | | 45 | 6·16 | | | | | | |

* H. C. Brown, McDaniel, and Hatliger, "Dissociation Constants" in Braude and Nachod, "Determination of Organic Structures by Physical Methods," Academic Press Inc., New York, 1955. [b] Gero and Markham, *J. Org. Chem.*, 1951, **16**, 1835. [c] Bruehlman and Verhoek, *J. Amer. Chem. Soc.*, 1948, **70**, 1401. [d] D. A. Brown and M. J. S. Dewar, *J.*, 1953, 2406. [e] Briegleb, *Z. Elektrochem.*, 1949, **53**, 355.

* At 20°.

TABLE 2. *Thermodynamic functions for equilibrium reactions of type* (1) *at* 25°.

| No. | | $\Delta G$ (kcal. mole$^{-1}$) | $\Delta H$ (kcal. mole$^{-1}$) | $\Delta S$ (cal. deg.$^{-1}$ mole$^{-1}$) |
|---|---|---|---|---|
| 1 | Pyridine | −5·15 | −14·95 | −32·9 |
| 2 | 2-Methylpyridine | −0·65 | −12·83 | −40·9 |
| 3 | 3-Methylpyridine | −5·32 | −15·17 | −33·1 |
| 4 | 4-Methylpyridine | −6·03 | −15·65 | −32·3 |
| 5 | 2 : 4-Dimethylpyridine | −1·39 | −13·64 | −41·2 |
| 6 | 2 : 5-Dimethylpyridine | −0·74 | −12·58 | −39·7 |
| 7 | 2 : 6-Dimethylpyridine | −1·43 | −13·64 | −41·0 |
| 8 | Quinoline | −2·84 | −15·80 | −43·5 |
| 9 | *iso*Quinoline | −5·15 | −14·13 | −30·1 |
| 10 | Piperidine | −7·76 | −13·88 | −20·5 |
| 11 | Pyrrolidine | −9·33 | −14·94 | −18·8 |

nitrogen atom is the main factor determining the co-ordinating ability of the pyridine bases toward the (diacetyl bisbenzoylhydrazone)nickel(II) as well as the proton. That log $K$ for 2-picoline is much smaller than that expected on the basis of its proton affinity can be ascribed to an $F$-strain between its methyl group and the plane of the Ni(DBH).

This hindrance, of course, is absent when the reference acceptor is the proton. The same *F*-strain would account for the lower values of log *K* for all the 2-substituted pyridines of the second group.

*R* for quinoline, 0·43, is much higher than those of the other 2-substituted bases (0·08—0·15), and reflects a significant structural difference between quinoline and the 2-substituted pyridines. In fact the planar molecules of the aromatic bases which co-ordinate to the nickel atom will tend to arrange themselves in one of the two planes perpendicular to the co-ordination plane of the nickel(II) atom so as to bisect one of the N–Ni–O and N–Ni–N bond angles. Thus the hydrogen atom of the *ortho* C–H group of the quinoline can come between two adjacent ligand atoms. In the case of 2-picoline, on the other hand, the free rotation of the 2-methyl group prevents any hydrogen atom of the methyl group from penetrating easily between two adjacent co-ordinated atoms. As a consequence the approach of the base to the central nickel atom will be hindered.

Acridine does not produce a change in colour of the benzene solution of (diacetyl bisbenzoylhydrazone)nickel(II). This is rather surprising because the nitrogen atom has a fairly high electron density ($Q_N = 1{\cdot}431$) and it is a good base ($pK_H = 5{\cdot}60$ at 20°). It is even more remarkable in view of the fact that 2 : 6-lutidine does actually form an adduct.

The value of *R* for the piperidine complex is smaller than that for the pyridine complex (0·512 and 0·732 respectively), probably owing, at least in part, to the smaller size of the pyridine molecule. However, the piperidine and pyridine complexes of silver(I) have ratios, *R'*, which are related to the corresponding ones in the Ni(DBH) system, *R*, by a factor which is very close to 1·4 in each case. There is evidence that π-bonds are formed between silver and heterocyclic bases [9] and in view of the striking similarity in the ratio of *R* to *R'*, and despite the two systems' being so different, π-bonds are probably operative also in the case of Ni(DBH),2Base. This could contribute to a value of *R* which is larger in the case of the pyridine complex than in that of the piperidine complex.

*Heat of Reaction.*—A negative value of $\Delta G$ is essential to form a stable complex so it is of great assistance if $\Delta H$ is negative; our values range from −12·58 to −15·81 kcal. mole$^{-1}$. This small change in $\Delta H$ shows that the largest part in the change in $\Delta G$ is in $\Delta S$ of the reactions.

The values of $\Delta H$ for the 2-substituted pyridines (−12·58 to −13·64 kcal. mole$^{-1}$) are lower than those for the other substituted pyridines (−14·13 to −15·80 kcal. mole$^{-1}$). If $\Delta H$ is considered to measure bond strength this difference confirms the presence of steric hindrance in the formation of adducts of 2-substituted pyridines.

*Entropy Changes.*—Table 2 shows that the entropy changes for the formation of the hexaco-ordinate complexes are always negative, the values of $\Delta S$ ranging from −18·8 to −43·5 e.u. A negative entropy is expected for a system such as this where (i) the number of free particles decreases and (ii) the nickel complex and the aromatic base lose independent motion upon combination. The values of $\Delta S$ can be collected in two groups: one group of the secondary amines with $\Delta S$ −18·8 and −20·5, and another group of the pyridine bases with $\Delta S$ −30·1 to −43·5 e.u. This large difference between the two sets of values can be accounted for in terms of a reduction in the freedom of rotation of the pyridine bases around the Ni–N bond with respect to that of piperidine and pyrrolidine. Indeed, if double-bonding is involved in the bonds between nickel and the nitrogen of the pyridine bases, it should result in a hindrance of rotation of the amine. This loss in entropy therefore corroborates the hypothesis of π-bond character of such co-ordinate links.

The values of $\Delta S$ for the pyridine bases can be further subdivided into two groups. The former, from −39·7 to −43·5, correspond to all the *ortho*-substituted pyridines; the second, from −30·1 to −33·1, refers to the non-*ortho*-substituted pyridine bases. The large negative entropy changes for the *ortho*-substituted pyridines can be attributed to a

[9] Chatt and Williams, *J.*, 1951, 3061; 1954, 4403; Chatt, Duncanson, and Venanzi, *J.*, 1955, 4456; Murman and Basolo, *J. Amer. Chem. Soc.*, 1955, **74**, 3484.

restriction of free rotation of the *ortho*-methyl group about the C–C bond due to the penetration of a hydrogen atom of the methyl group between two adjacent ligand atoms of the plane of the nickel central atom. This "*ortho*-effect," already verified also for the entropies of hydration of the same substituted pyridines,[10] appears probably as an important factor in determining the rigidity of the octahedral complex molecules.

We are indebted to the Italian "Consiglio Nazionale delle Ricerche" for financial support.

ISTITUTO DI CHIMICA GENERALE DELL'UNIVERSITÀ,
PALERMO, ITALY. [*Received, August 22nd,* 1957.]

[10] Andon, Cox, and Herington, *J.*, 1954, 3188.

---

## 165. *The Alkylation of Mercaptobenzothiazole.*

By K. J. MORGAN.

Further alkylation of the isomeric *N*- and *S*-alkyl derivatives of mercaptobenzothiazoles has been investigated, and spectral data used to establish the structure of the products. The formation of anomalous products can be explained by the thermal dissociation of the salts. The structure and spectra of the corresponding acid salts of 2-alkylthiobenzothiazoles are discussed.

DIRECT alkylation of mercaptobenzothiazole leads to alkylthiobenzothiazoles;[1] the isomeric *N*-alkyl derivatives are prepared less directly. Both types of compound give salts on further alkylation with alkyl iodide or alkyl sulphate. The product from ethyl iodide and 2-methylthiobenzothiazole has been reported[2] to be identical with that formed from methyl iodide and 2-ethylthiobenzothiazole; Fry and Kendall[3] suggested that in both cases the product was 3-methyl-2-methylthiobenzothiazolium iodide which was isolated from the mixture of all possible products of transalkylation of 2-alkylthiobenzothiazole with the salt initially formed. The evidence available was largely that of melting points, notoriously unreliable with these compounds, and analyses of crude products. To obtain more precise results infrared and ultraviolet spectra of the products have been examined and correlated; the results have in part confirmed and also extended those reported previously.

(I) (II)

The mode of formation and the close similarity of the ultraviolet spectra (Table 1) strongly suggest that the salts are *NS*-dialkyl compounds (I). This is confirmed by the existence of only one dimethyl iodide and only one diethyl iodide but of two ethylmethyl iodides. To account for the formation of anomalous products it has been suggested[4] that the initial product of the addition of alkyl iodide to 2-alkylthiobenzothiazoles is the sulphonium salt, (Benzothiazolyl)RR'S$^+$ I$^-$, which undergoes carbonium-ion rearrangement; similar intermediates have been postulated for the halogen-catalysed isomerisation of 2-alkylthiobenzothiazoles to the thermodynamically more stable *N*-alkyl isomers.[5]

[1] Hunter, *J.*, 1930, 123; Reed, Robertson, and Sexton, *J.*, 1939, 473.
[2] Sexton, *J.*, 1939, 470.
[3] Fry and Kendall, *J.*, 1951, 1716.
[4] Davies and Sexton, *J.*, 1942, 304; Mann and Watson, *J. Org. Chem.*, 1948, **13**, 502.
[5] Moore and Waight, *J.*, 1952, 4237.

The isolation of distinct salts [(I; R = Me, R′ = Et) and (I; R = Et, R′ = Me)] from 2-ethylthio- and 2-methylthio-benzothiazole, respectively, by using the appropriate alkyl iodide and a short reaction time excludes such intervention. The primary product is apparently formed by alkylation at the free hetero-atom. The mixtures, obtained from attempts to raise the yield of these salts by longer heating, may accordingly be ascribed to some further reaction of the primary product. Thus when a longer reaction time (*e.g.*, the conditions used by Beilenson and Hamer [6]) is used, in both cases the product isolated by by the normal method is the *NS*-dimethyl iodide (see Experimental).

TABLE 1. *Ultraviolet absorption spectra.*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Benzothiazole | λ(mμ) | — | 256 | 285 | 294 | — | — |
| | log ε | — | 3·76 | 3·22 | 3·13 | — | — |
| 2-Thiobenzothiazoline | λ(mμ) | [235] | [252] | [282] | — | — | 320 |
| | log ε | 4·12 | 3·82 | 3·34 | — | — | 4·43 |
| 3-Methyl-2-thiobenzothiazoline | λ(mμ) | 241 | [255] | [283] | — | — | 324 |
| | log ε | 4·12 | 3·82 | 3·41 | — | — | 4·41 |
| 3-Ethyl-2-thiobenzothiazoline | λ(mμ) | 242 | [255] | [283] | — | — | 324 |
| | log ε | 4·47 | 4·1 | 3·2 | — | — | 4·7 |
| 2-Methylthiobenzothiazole | λ(mμ) | 244 | — | 278 | 288 | 299 | — |
| | log ε | 3·94 | — | 4·1 | 4·03 | 3·92 | — |
| 2-Ethylthiobenzothiazole | λ(mμ) | [245] | — | 280 | [290] | 302 | — |
| | log ε | 3·9 | — | 4·06 | 4·0 | 3·9 | — |
| 3-Methyl-2-methylthiobenzothiazolium iodide | λ(mμ) | — | 257 | — | — | 306 | — |
| | log ε | — | 3·85 | — | — | 4·18 | — |
| 3-Ethyl-2-methylthiobenzothiazolium iodide ... | λ(mμ) | — | 258 | — | — | 308 | — |
| | log ε | — | 3·85 | — | — | 4·14 | — |
| 2-Ethylthio-3-methylbenzothiazolium iodide ... | λ(mμ) | — | 258 | — | — | 305 | — |
| | log ε | — | 3·78 | — | — | 4·1 | — |
| 3-Ethyl-2-ethylthiobenzothiazolium iodide ... | λ(mμ) | — | 258 | — | — | 307 | — |
| | log ε | — | 3·75 | — | — | 4·03 | — |

Figures in [square] brackets refer to points of inflexion.

Examination of the conditions leading to transalkylation showed that the *S*-alkyl group in the *NS*-dialkyl iodides could be replaced by heating them with alkyl iodide. Further, an alkylating action entirely analogous to that of the alkyl iodides is shown by the salts themselves: inaddit ion to *N*-alkylation [3] of free 2-alkylthiobenzothiazoles *S*-alkylation of *N*-alkyl thiones, and *S*-alkyl exchange between mixtures of salts occur. However, when an attempt was made to equilibrate a mixture of the two *NS*-ethyl-methyl iodides in an open flask the product contained no salt but was a mixture of the two *N*-alkyl thiones. While the pure salts were stable to prolonged heating in sealed tubes, when heated in open vessels they gave quantitative yields of the appropriate thione and alkyl iodide was liberated; to this may be attributed the alkylating action previously [3] associated with the salts themselves. Production of mixtures of salts may be expected to follow from re-alkylation of the thione to a salt which will in general differ from that formed initially until a state of dynamic equilibrium is reached. Such a mechanism may also operate in the isomerisation, catalysed by alkyl halide, of 2-alkylthiobenzothiazoles to the *N*-alkyl thiones.

Mixtures were not formed in the other preparations of the *NS*-ethyl-methyl salts investigated and in each case the product was that expected. The homogeneity of the salts formed from alkyl sulphates can be ascribed to the mild reaction conditions. The stability of the *N*-alkyl group makes the salts formed by direct alkylation of the *N*-alkyl thiones insensitive to subsequent reaction. In these alkylations methylation was easier than ethylation.

*Spectral Measurements.*—The ultraviolet spectra (Table 1) of the dialkylated salts are similar. Bands at 257 and 306 mμ can be assigned to benzene and thioamide absorption

[6] Beilenson and Hamer, *J.*, 1939, 143.

respectively;[7,8] similar bands are shown by many 2-thio-substituted benzothiazoles.[9] A long-wavelength band at 325 mμ is due to the conjugated thione group and is completely lacking in the spectra of the salts. The most important contributions to the structure of the salts probably arise from the benzothiazolium (I) rather than the sulphonium (II) form.

The infrared spectra of the salts are generally similar in form. Groups of bands common to many derivatives of benzothiazole are derived from the aromatic nucleus: C:C stretching (1455—1470, 1592—1608 cm.$^{-1}$), C·H deformation (743—767 cm.$^{-1}$), 1 : 2-di-substituted benzene (1013—1030, 1050—1060 cm.$^{-1}$), aromatic–nitrogen stretching (1307—1330 cm.$^{-1}$), and aromatic–sulphur stretching frequencies (703—709 cm.$^{-1}$). The assignment of a band at 1495 cm.$^{-1}$ in the spectrum of mercaptobenzothiazole to the N·C:S group[10] seems of doubtful validity; a corresponding band is found in the spectra of the *NS*-dialkyl salts (1502—1511 cm.$^{-1}$) but is absent from that of the *N*-alkyl thiones. The frequencies of bands in the range 700—1000 cm.$^{-1}$ are given in Table 2; this region was the most valuable for characterising the salts.

TABLE 2. *Infrared spectra (band frequencies in cm.$^{-1}$).*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2-Thiobenzothiazoline | 1000(w) | — | — | 938(w) | 869(w) | 851(w) | — |
| 3-Methyl-2-thiobenzothiazoline | — | 966(s) | — | 928(m) | — | — | 823(w) |
| 3-Ethyl-2-thiobenzothiazoline | 997(s) | — | — | 935(w) | 919(m) | 849(m) | 833(w) |
| 2-Methylthiobenzothiazole | 1009(s) | 974(w) | 961(m) | 928(w) | 904(w) | 855(w) | — |
| 2-Ethylthiobenzothiazole | 995(s) | 971(w) | — | 931(w) | — | 849(w) | — |
| 3-Methyl-2-methylthiobenzothiazolium iodide | — | 976(m) | 952(w) | — | 893(w) | 851(w) | 816(m) |
| 3-Ethyl-2-methylthiobenzothiazolium iodide | 988(m) | 976(m) | 957(w) | 927(w) | — | 857(w) | — |
| 2-Ethylthio-3-methylbenzothiazolium iodide | 994(m) | 966(w) | — | — | — | — | 818(m) |
| 3-Ethyl-2-ethylthiobenzothiazolium iodide | — | 976(w) | — | 929(w) | — | — | 840(w) |
| 2-Methylthiobenzothiazolium iodide | 988(m) | 973(m) | 952(w) | — | 869(w) | 855(w) | — |
| 2-Ethylthiobenzothiazolium iodide | 996(m) | 977(w) | 952(w) | — | — | 859(w) | 812(m) |
| 2-Ethylthiobenzothiazolium perchlorate | 994(w) | — | 952(w) | 923(w) | — | 862(w) | — |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2-Thiobenzothiazoline | — | — | 751(s) | — | 719(m) | 707(w) |
| 3-Methyl-2-thiobenzothiazoline | — | — | 749(s) | — | 717(m) | 709(w) |
| 3-Ethyl-2-thiobenzothiazoline | 779(m) | — | 743(s) | — | 718(m) | 709(w) |
| 2-Methylthiobenzothiazole | — | 765(s) | 758(s) | 727(m) | 722(m) | 707(w) |
| 2-Ethylthiobenzothiazole | — | — | 754(s) | 728(s) | — | 705(w) |
| 3-Methyl-2-methylthiobenzothiazolium iodide | — | — | 756(s) | — | — | 712(m) |
| 3-Ethyl-2-methylthiobenzothiazolium iodide | 786(m) | 767(s) | — | — | 720(m) | 715(w) |
| 2-Ethylthio-3-methylbenzothiazolium iodide | 796(w) | 762(s) | — | — | — | 715(m) |
| 3-Ethyl-2-ethylthiobenzothiazolium iodide | 789(w) | 768(s) | 759(m) | — | 724(w) | 711(w) |
| 2-Methylthiobenzothiazolium iodide | 778(m) | — | 752(s) | — | 721(w) | 707(w) |
| 2-Ethylthiobenzothiazolium iodide | — | — | 757(s) | — | 722(w) | 707(w) |
| 2-Ethylthiobenzothiazolium perchlorate | — | — | 762(s) | — | 720(m) | 711(w) |

*Spectra and Structure of the Acid Salts of 2-Alkylthiobenzothiazoles.*—2-Alkylthiobenzothiazoles react with hydriodic acid to give crystalline salts whose spectral characterisation presents several points of interest. Attempts to measure the ultraviolet spectra in solution in alcohol or acetic acid led only to the spectra of the free bases. Attempts to measure the ultraviolet spectrum of 2-ethylthiobenzothiazolium perchlorate gave similar results in alcohol but in 0·1N-perchloric acid in acetic acid the spectrum ($\lambda_{max.}$ 311 mμ, log ε 3·95) was closely similar to those of the dialkyl salts. The infrared spectrum of the perchlorate showed many of the bands found in the spectra of the *NS*-dialkyl salts (Table 2); in addition a new band at 3096 cm.$^{-1}$ (in Nujol) was observed in a position appropriate to an N$^{+}$·H stretching frequency.[11] The perchlorate can thus be regarded as structurally analogous to the *NS*-dialkylated compounds. The spectra of the hydriodides in the

[7] Morton and Stubbs, *J.*, 1939, 1321.
[8] Cerniani and Passerini, *J.*, 1954, 2261.
[9] Barltrop and Morgan, *J.*, 1957, 3072.
[10] Mann, *Trans. Inst. Rubber Ind.*, 1951, **27**, 232.
[11] Thompson, Nicholson, and Short, *Discuss. Faraday Soc.*, 1950, **9**, 222.

single-bond stretching region differ markedly from that of the perchlorate though they show a general similarity over the rest of the spectrum. The weak $N^+$·H stretching band is missing and is replaced by a strong broad band at 2674 and 2551 cm.$^{-1}$ in the methylthio- and ethylthio-salts, respectively. This region is associated with the S·H stretching frequency but it is highly improbable that a sulphonium salt would give rise to bands of such intensity. Bands in this region are also found in the spectra of amino-[12] and amido-acids where they have been attributed to overtone or combination bands.[13] Closer analogies are provided by triethylammonium halides, all four of which show bands at 2540 cm.$^{-1}$ differing only in their fine structure,[14] and by pyridinium chloride (though not the iodide) which has a similar band at 2450 cm.$^{-1}$. These bands have been assigned[14] to a strong $N^+$–H···$X^-$ hydrogen bond. A band at 2577 cm.$^{-1}$ in the spectrum of *o*-phenylenediamine perchlorate is of interest since the perchlorate ion is not normally hydrogen bonded; the band may be attributed to intramolecular hydrogen bonding and a similar explanation may account for the band found in the spectra of amino-acids. Accordingly, in the spectra of 2-alkylthiobenzothiazolium iodides the band may be assigned to an $N^+$·H vibration and these salts can be given structures analogous to those of the *NS*-dialkyl iodides. Further support was provided by the spectra of the hydriodides in dioxan (none of the usual liquids was a solvent for these salts) in which a band at 3378 cm.$^{-1}$ is indicated.

3-Methyl-2-thiobenzothiazoline has been reported[15] to give a chloroplatinate. No signs of salt formation could be detected when the *N*-alkyl thiones or mercaptobenzothiazole itself was treated with acids; their spectra remained unchanged even in perchloric–acetic acid.

## Experimental

*2-Alkylthiobenzothiazoles.*—2-Methylthiobenzothiazole, b. p. 116°/0·5 mm., m. p. 49° [hydriodide, m. p. 179—181° (decomp.)], and 2-ethylthiobenzothiazole, b. p. 114°/1 mm., m. p. 26° [hydriodide, m. p. 149—150° (decomp.) (Found: C, 33·3; H, 3·4. Calc. for $C_9H_{10}NS_2I$: C, 33·4; H, 3·1%), *perchlorate*, m. p. 137—138° (Found: C, 34·2; H, 3·2. $C_9H_{10}O_4NS_2Cl$ requires: C, 34·4; H, 3·3%)], were prepared from mercaptobenzothiazole.[1]

*3-Alkyl-2-thiobenzothiazoline.*—3-Methyl-2-thiobenzothiazoline, b. p. 156°/0·5 mm., m. p. 96°, and 3-ethyl-2-thiobenzothiazoline, m. p. 79·5—80·5°, were prepared from *NS*-dimethyl and -diethyl sulphates, respectively.[2]

*3-Alkyl-2-alkylthiobenzothiazolium Iodides.*—(*a*) The *NS*-dimethyl iodide, m. p. 146—147° (decomp.), was prepared from methyl iodide or methyl sulphate–potassium iodide[2] and both 2-methylthiobenzothiazole and 3-methyl-2-thiobenzothiazoline (Found: C, 33·9; H, 2·9. Calc. for $C_9H_{10}NS_2I$: C, 33·4; H, 3·1%). (*b*) *NS*-Diethyl iodide, m. p. 119·5—120·5° (decomp.) was obtained by four entirely analogous preparations (Found: C, 37·6; H, 4·4. Calc. for $C_{11}H_{14}NS_2I$: C, 37·6; H, 4·4%). (*c*) Methylation of the *N*-ethyl thione or the action of ethyl sulphate–potassium iodide on 2-methylthiobenzothiazole led to 3-ethyl-2-methylthiobenzothiazolium iodide, m. p. 132—134° (decomp.) (Found: C, 35·5; H, 3·5; N, 4·2. Calc. for $C_{10}H_{12}NS_2I$: C, 35·6; H, 3·6; N, 4·2%), which was decomposed by sodium sulphide to the *N*-ethyl thione and methanethiol (mercury derivative,[16] m. p. 173°). (*d*) 2-Ethylthio-3-methylbenzothiazolium iodide, m. p. 137—138° (decomp.), was prepared by three methods entirely analogous to those described above (*c*) (Found: C, 35·3; H, 3·6%); with sodium sulphide it gave *N*-methyl-thione and ethanethiol (mercury derivative,[17] m. p. 75°).

*Action of Methyl Iodide on 2-Ethylthiobenzothiazole.*—(*a*) Ethylthiobenzothiazole (2·3 g.) when refluxed with methyl iodide (2·3 g.) for 2 hr. gave a mixture which after two crystallisations from methanol left the *NS*-dimethyl iodide, m. p. 143—145° (decomp.), mixed m. p. 144—145°

[12] Randall, Fowler, Fuson, and Dangl, "Infrared Determination of Organic Structures," Van Nostrand, New York, 1949.
[13] Fuson, Josien, and Powell, *J. Amer. Chem. Soc.*, 1952, **74**, 1.
[14] Lord and Merrifield, *J. Chem. Phys.*, 1953, **21**, 166.
[15] Mohlau and Klopfer, *Ber.*, 1898, **31**, 3164.
[16] Klason, *Ber.*, 1887, **20**, 3410.
[17] *Idem*, *J. prakt. Chem.*, 1877, **15**, 205.

(decomp.), whose spectrum was identical with that of an authentic specimen (Found: C, 33·8; H, 3·4%). Degradation of the salt with sodium sulphide gave the *N*-methyl thione and methanethiol. (*b*) A mixture of the same reagents was heated for 30 min. Two crystallisations (from methanol) of the crude product gave 2-ethylthio-3-methylbenzothiazolium iodide, m. p. 134—136° (decomp.); its identity was confirmed by the infrared spectrum.

*Action of Ethyl Iodide on 2-Methylthiobenzothiazole.*—(*a*) This reaction [6] gave the *NS*-dimethyl iodide, m. p. 144—145° (decomp.). (*b*) When the reaction time was only 1 hr. a small yield of 3-ethyl-2-methylthiobenzothiazolium iodide, m. p. 132—134° (decomp.) (from methanol), was obtained; its identity was confirmed by the infrared spectrum.

*Action of Heat on the Salts.*—(*a*) 3-Ethyl-2-methylthiobenzothiazolium iodide was recovered after being heated in a sealed tube at 100° for 22 hr. 2-Ethylthio-3-methylbenzothiazolium iodide was similarly stable under these conditions. (*b*) A mixture of these salts (200 mg. of each) was heated in a sealed tube at 100° for 18 hr. From the product the *NS*-dimethyl iodide, m. p. 145—146° (decomp.), was isolated. (*c*) A similar mixture of salts was heated at 100° for 18 hr. under an air condenser closed only by a drying tube. The mixture of products, m. p. 58—67°, was completely soluble in benzene; in methanol it showed $\lambda_{max.}$ 325 mμ (log ε 4·8). (*d*) Each salt (150 mg.) was heated separately at 100°/10 mm. for 18 hr. to give a quantitative yield of the corresponding thione. The volatile product from the decomposition of the *NS*-dimethyl iodide was washed with pyridine; evaporation of excess of pyridine left pyridine methiodide, m. p. 116° (decomp.).

*Action of Alkyl Iodide on the Salts.*—2-Ethylthio-3-methylbenzothiazolium iodide (1 g.) was heated in a sealed tube at 100° for 18 hr. with methyl iodide (0·15 c.c.). The residue was washed with ether to leave the *NS*-dimethyl iodide, m. p. 144—145° (decomp.). 3-Ethyl-2-methylthiobenzothiazolium iodide, m. p. 132—134° (decomp.), was obtained similarly from the *NS*-diethyl iodide.

*Action of the Salts on Alkyl Derivatives of Mercaptobenzothiazole.*—(*a*) The *NS*-dimethyl iodide (1 g.) was heated in a sealed tube with 2-methylthiobenzothiazole (5 g.) at 100° for 18 hr. to give the *N*-methyl thione [3] (1·5 g.), m. p. 96°. The *NS*-dimethyl iodide (500 mg.), m. p. 145—146° (decomp.), was recovered. (*b*) 3-Ethyl-2-methylthiobenzothiazolium iodide (400 m.g.) was allowed to equilibrate with the *N*-methyl thione (300 mg.) for 18 hr. at 100°. The product was washed with benzene (2 × 5 c.c.); the residue was the *NS*-dimethyl iodide, m. p. 145—146° (decomp.). The benzene washings contained a mixture of thiones ($\lambda_{max.}$ 327 mμ) which was fractionated into the *N*-methyl thione, m. p. 91°, and the *N*-ethyl thione, m. p. 80°. Similar results were obtained when the *NS*-diethyl iodide was heated with the *N*-methyl thione.

*Hydrolysis of 2-Alkylthiobenzothiazolium Iodides.*—An attempt was made to decompose 2-ethylthio- and 2-methylthio-benzothiazolium iodides with sodium sulphide. In each case hydrolysis of the salt was complete before the reagent was added to the warm aqueous solution; the parent base was recovered quantitatively.

*Spectra.*—Ultraviolet spectra were measured in methanol unless otherwise stated on a Beckman D.U. and a Unicam S.P. 500 spectrometer. Infrared spectra were measured on a Perkin–Elmer self-recording instrument; specimens were prepared as mulls with Nujol or discs with potassium chloride.

This work was performed during the tenure of a Civil Service Senior Research Fellowship. The author thanks the Chief Scientist, Ministry of Supply, for permission to publish these results, Mr. J. Hatcher and Mr. F. Hastings for the infrared spectra, and Mr. F. E. Charlton for some analyses.

Chemical Defence Experimental Establishment,
Porton, Wiltshire.

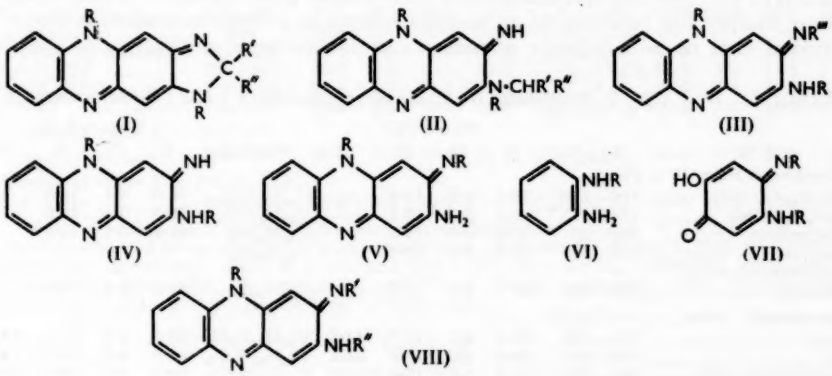
[*Received, September 9th*, 1957.]

## 166. *The Oxidation of Derivatives of* o-*Phenylenediamine. Part V.*[1] $N^3$-*Substituted Derivatives of Anilino*apo*safranine* (*Rimino-compounds*) *and Related Compounds.*

By Vincent C. Barry, J. G. Belton, J. F. O'Sullivan, and Dermot Twomey.

Catalytic hydrogenation of glyoxalinophenazines [1] yields $N^3$-substituted derivatives of anilino*apo*safranines (rimino-compounds) and not $N^2$-substituted derivatives as stated earlier.[1] Some of these compounds, and others not accessible by the glyoxalinophenazine route, have been prepared by reaction of primary amines with anilino*apo*safranines. Similar compounds have also been obtained by condensation of isomers [2] of anilino*apo*safranines with some primary amines and by condensation of 4 : 5-diarylamino-*o*-quinones with *o*-phenylenediamines.[3]

We have described in Part IV [1] the hydrogenation of dihydrogloxalinophenazines (I) which resulted in the opening of the glyoxaline ring and formation of derivatives to which we assigned structure (II). The presence of =NH in these compounds was suggested by their relative instability in boiling acetic anhydride and the appearance of a sharp band at 3300 cm.$^{-1}$ in the infrared region. Further examination of the infrared spectra of these and related compounds has shown that this band is due to an $-NH-$ group. Again, deductions based on the results of bromination of these compounds are now known to be of doubtful validity, as a continuing investigation of the bromination of a variety of related phenazines has shown the situation to be very complex. It is now clear that formula (II) does not represent the structure of these "rimino-compounds" and that hydrogenation results in the opening of the 1' : 2'-bond of the glyoxalino-ring giving




compounds of structure (III). We have also shown that compound (III; R = Ph, R''' = Pr$^i$) may be recyclised to the glyoxalino-compound (I; R = Ph, R' = R'' = Me) by heating it in nitrobenzene under reflux. Identical compounds (III) have been obtained by treating anilino*apo*safranine with appropriate primary alkyl- and *cyclo*alkylamines. For example, compound (III; R = Ph, R''' = Pr$^i$) has been obtained from the glyoxalino-compound (I; R = Ph, R' = R'' = Me) and also by heating anilino*apo*safranine with *iso*propylamine.

Further, heating anilino*apo*safranine (IV; R = Ph) with aniline yields the compound

[1] Part IV, Barry, Belton, O'Sullivan, and Twomey, *J.*, 1956, 3347.
[2] *Idem*, *J.*, 1956, 896.
[3] Kehrmann and Cordone, *Ber.*, 1913, **46**, 3009.

(III; R = R''' = Ph) which has been synthesised unambiguously by condensation of the amine (VI; R = Ph) with the quinone imine (VII; R = Ph). By analogy, therefore, it may be concluded that primary amines react with anilino*apo*safranines replacing the =NH by =NR. The absence of the =NH group from the substituted compounds (III) is also supported by their failure to react with 1-fluoro-2 : 4-dinitrobenzene.

Compound (III; R = R''' = Ph) has also been obtained by treating glyoxalino-compounds (I; R = Ph, R' = R'' = Me; and R = Ph, CR'R'' = *cyclo*hexane) with aniline under reflux, and under similar conditions from the substituted imines (III; R''' = alkyl or *cyclo*alkyl). It has also been obtained by refluxing the isomer (V; R = Ph) of anilino*apo*safranine with aniline, and thus this compound has now been made by five methods.

Certain substituted imines, *e.g.*, (III; R = Ph, R''' = Me), not accessible by the glyoxaline route, have been prepared by reaction of anilino*apo*safranines (IV) with primary aliphatic amines. The compound (III; R = Ph, R''' = Me) was also obtained by direct alkylation of compound (IV; R = Ph). Phenethylamine reacted as expected with anilino*apo*safranine. On the other hand, benzylamine gave a product which did not have the properties expected for compound (III; R = Ph, R''' = $CH_2Ph$): this product was unstable, showed a bright green fluorescence, had unique colour reactions, and failed to yield a crystalline material on hydrogenation; the analytical data fit the requirements of either the substituted imine or the glyoxalino-compound.

Compound (III; R = Ph, R''' = $CH_2$·OH) is readily obtained by warming gently an ethanolic solution of anilino*apo*safranine (IV; R = Ph) with formaldehyde; it is unstable and decomposes in warm ethanol.

The reaction of anilino*apo*safranines (IV) with primary aromatic amines yielded some unexpected results. Thus, while heating compound (IV; R = Ph) with aniline or *p*-chloroaniline yielded the substituted imines (III; R = Ph, R''' = Ph or *p*-$C_6H_4Cl$), the compound (IV; R = *p*-$C_6H_4Cl$) on treatment with aniline gave a product which, although melting sharply and behaving on an alumina column as a single substance, is shown by analytical data to be a mixture of mono- and di-chlorinated derivatives of structure

TABLE 1. 5 : 1' : 2' : 2'-*Substituted* 5 : 2'-*dihydroglyoxalino*(5' : 4'-2 : 3)*phenazines* (I).

| CR'R'' | M. p.* | Found (%) C | H | N | Cl | Formula | Required (%) C | H | N | Cl |
|---|---|---|---|---|---|---|---|---|---|---|
| *Compounds where* R = Ph. | | | | | | | | | | |
| CMe·$CH_2$·CO·$NEt_2$ | 168—170° | 76·1 | 6·2 | 14·0 | — | $C_{32}H_{31}ON_5$ | 76·6 | 6·4 | 14·0 | — |
| CMe·$CH_2$·COMe | 174—175 | 78·4 | 5·5 | 12·3 | — | $C_{29}H_{24}ON_4$ | 78·4 | 5·4 | 12·6 | — |
| *cyclo*Heptane | 296—297 | 81·6 | 6·2 | 12·3 | — | $C_{31}H_{28}N_4$ | 81·6 | 6·1 | 12·3 | — |
| 4-Methyl*cyclo*hexane | 317—318 | 81·5 | 6·4 | 12·2 | — | $C_{31}H_{28}N_4$ | — | — | — | — |
| 3 : 5-Dimethyl*cyclo*-hexane | 288—289 | 81·7 | 6·5 | 11·9 | — | $C_{32}H_{30}N_4$ | 81·7 | 6·4 | 11·9 | — |
| *Compounds where* R = *p*-$C_6H_4Cl$. | | | | | | | | | | |
| CMeEt | 174—176 | 69·5 | 4·7 | 11·7 | 14·5 | $C_{28}H_{22}N_4Cl_2$ | 69·3 | 4·5 | 11·5 | 14·6 |
| $CEt_2$ | 179—181 | 69·9 | 4·9 | 11·4 | 14·4 | $C_{29}H_{24}N_4Cl_2$ | 69·7 | 4·8 | 11·2 | 14·2 |
| *cyclo*Heptane | 290—292 | 71·0 | 5·0 | 10·4 | 13·7 | $C_{31}H_{26}N_4Cl_2$ | 70·9 | 5·0 | 10·7 | 13·5 |
| 4-Methyl*cyclo*hexane | 277—279 | 70·8 | 4·7 | 10·7 | 13·6 | $C_{31}H_{26}N_4Cl_2$ | — | — | — | — |
| 3 : 5-Dimethyl*cyclo*-hexane | 267—269 | 71·0 | 5·2 | 10·6 | 13·5 | $C_{32}H_{28}N_4Cl_2$ | 71·2 | 5·2 | 10·4 | 13·2 |
| *Compound where* R = *o*-$C_6H_4Cl$. | | | | | | | | | | |
| $CMe_2$ | 217—218 | 68·6 | 4·2 | 11·9 | 14·8 | $C_{27}H_{20}N_4Cl_2$ | 68·8 | 4·2 | 11·9 | 15·1 |

* All the compounds in this Table were recrystallised from benzene.

(VIII; R = R'' = *p*-$C_6H_4Cl$, R' = Ph; and R = *p*-$C_6H_4Cl$, R' = R'' = Ph). This indicates that the *p*-chloroaniline residue in the 2-position is to some extent replaceable by aniline under these conditions.

A similar result was obtained with the isomers (V) of anilino*apo*safranines. Compound (V; R = Ph) on treatment with aniline gave compound (III; R = R''' = Ph) in high

TABLE 2. N³-*Substituted anilino*aposafranine *derivatives* (III).

| | | Found (%) | | | | | Required (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| R‴ | M. p.* | C | H | N | Cl | Formula | C | H | N | Cl |
| *Compounds where* R = Ph. | | | | | | | | | | |
| Me | 180—181° | 79·4 | 5·5 | 14·6 | — | $C_{25}H_{20}N_4$ | 79·8 | 5·3 | 14·9 | — |
| Et | 182—183 | 79·8 | 5·8 | 13·9 | — | $C_{26}H_{22}N_4$ | 80·0 | 5·6 | 14·4 | — |
| Pr$^n$ | 173—175 | 80·2 | 5·9 | 13·9 | | $C_{27}H_{24}N_4$ | 80·2 | 5·9 | 13·9 | — |
| Bu$^n$ | 147—149 | 80·2 | 6·5 | 13·5 | — | $C_{28}H_{26}N_4$ | 80·4 | 6·2 | 13·4 | — |
| Bu$^i$ | 160—161 | 80·6 | 6·4 | 13·4 | — | $C_{28}H_{26}N_4$ | | | | |
| Bu$^t$ | 189—190 | 80·3 | 6·0 | 13·5 | — | $C_{28}H_{26}N_4$ | | | | |
| $n$-$C_5H_{11}$ | 143—145 | 80·4 | 6·5 | 13·3 | — | $C_{29}H_{28}N_4$ | 80·6 | 6·5 | 13·0 | — |
| $n$-$C_7H_{15}$ | 130—131 | 80·8 | 6·7 | 12·2 | — | $C_{31}H_{32}N_4$ | 80·9 | 7·0 | 12·2 | — |
| 3 : 5 : 5-Trimethylhexyl | 131—133 | 81·2 | 7·5 | — | — | $C_{32}H_{36}N_4$ | 81·2 | 7·4 | — | — |
| $n$-$C_{10}H_{21}$ | 92—94 | 81·1 | 7·8 | 11·2 | — | $C_{34}H_{38}N_4$ | 81·3 | 7·6 | 11·2 | — |
| $n$-$C_{12}H_{25}$ | 95—96 | 81·1 | 8·0 | 10·3 | — | $C_{36}H_{42}N_4$ | 81·5 | 7·9 | 10·6 | — |
| 3 : 5-Dimethyl*cyclo*hexyl | 202—204 | 81·0 | 6·7 | 11·8 | — | $C_{32}H_{32}N_4$ | 81·3 | 6·8 | 11·9 | — |
| 4-Methyl*cyclo*hexyl | 175—177 | 81·0 | 6·5 | 12·1 | — | $C_{31}H_{30}N_4$ | 81·2 | 6·6 | 12·2 | — |
| *cyclo*Heptyl | 191—192 | 81·1 | 6·6 | 12·0 | — | $C_{31}H_{30}N_4$ | | | | |
| $CH_2$·OH | 154—156 | 76·5 | 5·3 | 13·9 | — | $C_{25}H_{20}ON_4$ | 76·5 | 5·1 | 14·3 | — |
| $CH_2$·$CH_2$·OH | 179—180 | 76·6 | 5·3 | 14·0 | — | $C_{26}H_{22}ON_4$ | 76·8 | 5·4 | 13·8 | — |
| $CH_2$·$CH_2$·$NEt_2$ | 137—139 | 77·0 | 6·7 | 14·4 | — | $C_{30}H_{31}N_5$ † | 77·0 | 6·9 | 14·3 | — |
| $CH_2$·$CH_2$Ph | 166—168 | 82·2 | 5·6 | 12·1 | — | $C_{32}H_{26}N_4$ | 82·4 | 5·6 | 12·0 | — |
| $p$-$C_6H_4Cl$ | 235—237 | 76·0 | 4·4 | 11·6 | 7·8 | $C_{30}H_{21}N_4Cl$ | 76·2 | 4·4 | 11·9 | 7·5 |
| *Compounds where* R = $p$-$C_6H_4Cl$. | | | | | | | | | | |
| Me | 224—225 | 66·8 | 4·1 | 12·1 | 15·8 | $C_{32}H_{18}N_4Cl_2$ | 67·4 | 4·0 | 12·6 | 16·0 |
| Et | 193—195 | 68·0 | 4·5 | 12·0 | 15·4 | $C_{33}H_{20}N_4Cl_2$ | 68·0 | 4·4 | 12·2 | 15·5 |
| Pr$^n$ | 200—201 | 68·4 | 4·7 | 11·9 | 15·0 | $C_{34}H_{22}N_4Cl_2$ | 68·5 | 4·7 | 11·8 | 15·0 |
| Bu$^n$ | 182—184 | 68·3 | 4·8 | 11·4 | 14·5 | $C_{35}H_{24}N_4Cl_2$ | 69·0 | 4·9 | 11·5 | 14·6 |
| Bu$^s$ | 199—201 | 69·1 | 5·1 | 11·7 | — | $C_{35}H_{24}N_4Cl_2$ | | | | |
| Bu$^i$ | 183—185 | 68·9 | 5·1 | 11·6 | 14·7 | $C_{35}H_{24}N_4Cl_2$ | | | | |
| $n$-$C_5H_{11}$ | 146—148 | 69·6 | 5·1 | 11·2 | 14·1 | $C_{36}H_{26}N_4Cl_2$ | 69·5 | 5·2 | 11·2 | 14·2 |
| $CHEt_2$ | 215—217 | 69·6 | 5·4 | 11·3 | 13·9 | $C_{36}H_{26}N_4Cl_2$ | | | | |
| $n$-$C_6H_{13}$ | 173—175 | 69·7 | 5·5 | 11·0 | 13·9 | $C_{36}H_{28}N_4Cl_2$ | 69·9 | 5·4 | 10·9 | 13·8 |
| $n$-$C_{10}H_{21}$ | 121—123 | 71·0 | 6·4 | — | 12·3 | $C_{40}H_{36}N_4Cl_2$ | 71·5 | 6·3 | 9·8 | 12·4 |
| $n$-$C_{12}H_{25}$ | 98—100 | 71·9 | 6·7 | 9·5 | 11·9 | $C_{42}H_{40}N_4Cl_2$ | 72·1 | 6·7 | 9·3 | 11·9 |
| 4-Methyl*cyclo*hexyl | 237—239 | 70·6 | 5·5 | 10·6 | 13·2 | $C_{37}H_{32}N_4Cl_2$ | 70·6 | 5·3 | 10·6 | 13·5 |
| *cyclo*Heptyl | 234 | 70·8 | 5·1 | 10·5 | 13·4 | $C_{37}H_{32}N_4Cl_2$ | — | — | — | — |
| 3 : 5-Dimethyl*cyclo*hexyl | 218—220 | 70·4 | 5·8 | 10·5 | 13·2 | $C_{38}H_{36}N_4Cl_2$ | 71·0 | 5·5 | 10·4 | 13·1 |
| $CH_2$·$CH_2$·OH | 207—208 | 65·6 | 4·4 | 12·0 | 14·8 | $C_{32}H_{26}ON_4Cl_2$ | 65·7 | 4·2 | 11·8 | 14·9 |
| $CH_2$·$CH_2$·$NEt_2$ | 158—160 | 67·4 | 5·3 | 13·2 | 13·4 | $C_{36}H_{36}N_5Cl_2$ | 67·9 | 5·5 | 13·2 | 13·4 |
| $p$-$C_6H_4Cl$ | 275—277 | 66·5 | 3·3 | 9·9 | 20·0 | $C_{30}H_{18}N_4Cl_2$ | 66·5 | 3·5 | 10·3 | 19·7 |
| *Compound where* R = $o$-$C_6H_4Cl$. | | | | | | | | | | |
| Pr$^i$ | 193—195 | 68·0 | 4·5 | 11·8 | 15·2 | $C_{37}H_{32}N_4Cl_2$ | 68·5 | 4·7 | 11·8 | 15·0 |
| *Compound where* R = $p$-$C_6H_4$·OMe. | | | | | | | | | | |
| $p$-$C_6H_4$·OMe | 219—221 | 75·3 | 5·4 | 10·7 | — | $C_{32}H_{28}O_2N_4$ | 75·0 | 5·3 | 10·6 | — |

* All the compounds in this Table were recrystallised from ethanol. † Solvate, $+\frac{1}{2}C_2H_5$·OH. The following ten compounds (III) have already been characterised (Table 2, Part IV [1]) but were formulated incorrectly: (III; R = Ph, and R‴ = Pr$^i$, Bu$^s$, $CHEt_2$, $CHMeBu^i$, *cyclo*hexyl or, $CHMe$·$[CH_2]_3$·OH); (III; R = $p$-$C_6H_4Cl$, and R‴ = Pr$^i$ or *cyclo*hexyl); (III; R = $p$-$C_6H_4Me$, R‴ = Pr$^i$); (III; R = $p$-$C_6H_4$·OPr$^i$, R‴ = *cyclo*hexyl).

TABLE 3.

| | | Found (%) | | | | | Required (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| R′ = R″ | M. p.* | C | H | N | Cl | Formula | C | H | N | Cl |
| *Compounds* (VIII; R = Me). | | | | | | | | | | |
| Ph | 205—206° | 79·5 | 5·6 | 15·0 | — | $C_{25}H_{20}N_4$ | 79·8 | 5·3 | 14·9 | — |
| $p$-$C_6H_4Cl$ | 245—246 | 67·3 | 4·1 | 12·6 | 16·0 | $C_{25}H_{18}N_4Cl_2$ | 67·4 | 4·0 | 12·6 | 16·0 |
| *Compounds* (VIII; R = $CH_2$·$CH_2$·$NEt_2$). | | | | | | | | | | |
| Ph | 146—147 | 78·2 | 6·9 | 15·3 | — | $C_{30}H_{31}N_4$ | 78·1 | 6·7 | 15·2 | — |
| $p$-$C_6H_4Cl$ | 168—169 | 67·8 | 5·5 | 13·4 | 13·6 | $C_{30}H_{29}N_4Cl_2$ | 67·9 | 5·5 | 13·2 | 13·4 |
| *Compounds* (VIII; R = *cyclo*hexyl). | | | | | | | | | | |
| Ph | 185—186 | 80·9 | 6·3 | 12·7 | — | $C_{30}H_{28}N_4$ | 81·1 | 6·3 | 12·6 | — |
| $p$-$C_6H_4Cl$ | 198 | 70·2 | 5·4 | 10·7 | 13·9 | $C_{30}H_{26}N_4Cl_2$ | 70·1 | 5·1 | 10·9 | 13·8 |
| *Compound* (VIII; R = $p$-$C_6H_4Cl$). | | | | | | | | | | |
| Ph | 205—206 | 75·8 | 4·5 | 12·3 | 7·8 | $C_{30}H_{21}N_4Cl$ | 76·2 | 4·4 | 11·9 | 7·5 |

* All compounds recrystallised from ethanol.

yield, but with *p*-chloroaniline a mixture similar to that described above was obtained. Again, treatment of compound (V; R = *p*-$C_6H_4Cl$) with aniline gave a mixture of mono- and di-chlorinated derivatives of sharp m. p., and not separable on alumina. When *p*-chloroaniline was used instead of aniline in this reaction, a single trichlorinated compound (III; R = R''' = *p*-$C_6H_4Cl$) resulted. It is clear, therefore, that compounds of structure (III) may be readily obtained in a pure state from structures (IV and V) when the reacting arylamine is the same as that already substituting in the 2- or 3-position of the phenazine nucleus.

The amine (V; R = Ph) does not react with alkyl- or *cyclo*alkyl-amines under reflux. At higher temperatures *cyclo*hexylamine reacts with compound (V; R = Ph), yielding compound (VIII; R = Ph, R' = R'' = *cyclo*hexyl). A similar result was obtained with the analogue (V; R = *p*-$C_6H_4Cl$).

Condensation of *o*-phenylenediamines and 4 : 5-diarylamino-*o*-quinones yields compounds of structure (VIII; R' = R'' = aryl, R = aryl, alkyl, *cyclo*alkyl, etc.) which, when R differs from R', are not accessible by any of the other routes described. In the preparation of the 4 : 5-diarylamino-*o*-quinones we have found sodium iodate to be a much more effective reagent than silver oxide.[3]

New glyoxalinophenazines are listed in Table 1 and the substituted imines in Tables 2 and 3. A preliminary account of the biological properties of these substituted imines has already been published.[4]

## Experimental

*2-Anilino-3 : 5-dihydro-3-methylimino-5-phenylphenazine.*—(a) *With methylamine.* Anilino*apo*safranine hydrochloride (4·0 g.) and 40% aqueous methylamine (20 c.c.) in ethanol (25 c.c.) were heated in a sealed tube at 130° for 3 hr. The dark red solid, recrystallised from ethanol (2·7 g.), had m. p. 180—181° (Found: C, 79·4; H, 5·5; N, 14·6. $C_{25}H_{20}N_4$ requires C, 79·8; H, 5·3; N, 14·9%). This *compound* has also been obtained, with m. p. 188—190°, from benzene. Its solution in concentrated sulphuric acid is petunia-purple, unchanged on dilution.

(b) *With methyl sulphate.* Anilino*apo*safranine (0·7 g.), methyl sulphate (0·7 c.c.), and 10% aqueous sodium hydroxide (3 c.c.) were heated under reflux in acetone (20 c.c.) for 4 hr. The solvent was removed and the product purified chromatographically in benzene on alumina. The product (0·3 g.) was identical with that obtained by method (a).

*2-Anilino-3 : 5-dihydro-3-hydroxymethylimino-5-phenylphenazine.*—Anilino*apo*safranine (0·6 g.), paraformaldehyde (1·6 g.), and ethanol (80 c.c.) were boiled for 3 min. The filtrate yielded orange yellow crystals (0·3 g.), m. p. 154—156° (from benzene) (Found: C, 76·5; H, 5·3; N, 13·9. $C_{26}H_{20}ON_4$ requires C, 76·5; H, 5·1; N, 14·3%).

*2-Anilino-3 : 5-dihydro-5-phenyl-3-phenyliminophenazine.*—This compound [3] was prepared by heating the hydrochloride of each of the following with aniline under reflux for 10 min.: (*a*) anilino*apo*safranine, (*b*) 2-amino-3 : 5-dihydro-5-phenyl-3-phenyliminophenazine, (*c*) 5 : 2'-dihydro-2' : 2'-dimethyl-5 : 1'-diphenylglyoxalino(5' : 4'-2 : 3)phenazine, (*d*) 2-anilino-3-*cyclo*hexylimino-3 : 5-dihydro-5-phenylphenazine. The cooled solutions were poured into ether and the precipitated salt converted into the base in each case. After chromatographic purification the product had m. p. 235—237° (from benzene). Yields were: from (*a*) and (*b*), 80%; from (*c*) and (*d*), 40%. The same compound was prepared by the condensation of 2-aminodiphenylamine hydrochloride and 4 : 5-dianilino-*o*-quinone.

4 : 5-*Di*-p-*chloroanilino*-o-*quinone*.—Catechol (4·4 g.) and *p*-chloroaniline (10·2 g.) were dissolved in ethanol (150 c.c.), and sodium iodate (8·0 g.) in water (150 c.c.) added. The mixture was stirred for 2 hr., then kept overnight; the dark red *quinone* (14·4 g.) which separated had m. p. 222—224° (from chloroform) (Found: C, 60·5; H, 3·4; N, 8·0; Cl, 20·0. $C_{18}H_{12}O_2N_2Cl_2$ requires C, 60·2; H, 3·3; N, 7·8; Cl, 19·8%).

4 : 5-*Di*-p-*toluidino*-o-*quinone*.—Prepared as above, this *quinone* formed bright red needles, m. p. 190—192°, from benzene (Found: C, 75·7; H, 5·7; N, 9·0. $C_{20}H_{18}O_2N_2$ requires C, 75·5; H, 5·7; N, 8·8%). The yield was theoretical.

2-p-*Chloroanilino*-3-p-*chlorophenylimino*-3 : 5-*dihydro*-5-*phenylphenazine*.—4 : 5-Di-*p*-chloroanilino-*o*-quinone (3·6 g.) and *N*-phenyl-*o*-phenylenediamine hydrochloride (2·2 g.) were heated

[4] Barry, Belton, Conalty, Denneny, Edward, O'Sullivan, Twomey, and Winder, *Nature*, 1957, **179**, 1013.

in ethanol (150 c.c.) under reflux for 1 hr. The mixture was made alkaline with ammonia and diluted with water. The *product* (2·3 g.) after chromatographic purification was obtained as dark red needles (from benzene), m. p. 241—242° (Found: C, 71·3; H, 3·7; N, 10·8; Cl, 14·0. $C_{30}H_{30}N_4Cl_2$ requires C, 71·0; H, 3·9; N, 11·0; Cl, 14·0%).

2-cyclo*Hexylamino*-3-cyclo*hexylimino*-3 : 5-*dihydro*-5-*phenylphenazine*.—2-Amino-3 : 5-dihydro-5-phenyl-3-phenyliminophenazine hydrochloride (3·0 g.) and *cyclo*hexylamine (35 c.c.) were heated in the autoclave at 185° for 1 hr. Unchanged *cyclo*hexylamine was removed by steam-distillation and the residual solid purified chromatographically on alumina. The *compound* (1·8 g.) was an orange powder, m. p. 188—190° (from ethanol) (Found: C, 79·9; H, 7·6; N, 12·8. $C_{30}H_{34}N_4$ requires C, 80·0; H, 7·6; N, 12·4%).

5-p-*Chlorophenyl*-2-cyclo*hexylamino*-3-cyclo*hexylimino*-3 : 5-*dihydrophenazine*.—2-Amino-5-*p*-chlorophenyl-3-*p*-chlorophenylimino-3 : 5-dihydrophenazine was treated with cyclo*hexyl*amine as in the previous experiment. The *product* was a brown-red powder, m. p. 196—198° (from ethanol) (Found: C, 73·8; H, 6·5; N, 11·5. $C_{30}H_{33}N_4Cl$ requires C, 74·3; H, 6·8; N, 11·6%).

2-p-*Chloroanilino*-5-p-*chlorophenyl*-3 : 5-*dihydro*-3-iso*propyliminophenazine*.—2-*p*-Chloroanilino-5-*p*-chlorophenyl-3 : 5-dihydro-3-iminophenazine hydrochloride (2·0 g.), *iso*propylamine (20 c.c.), and ethanol (40 c.c.) were heated for 2 hr. in the autoclave at 80°. The product, purified chromatographically, was identical with that obtained by catalytic hydrogenation of 5 : 1′-di-*p*-chlorophenyl-5 : 2′-dihydro-2′ : 2′-dimethylglyoxalino(5′ : 4′-2 : 3)phenazine.

2-p-*Chloroanilino*-5-p-*chlorophenyl*-3-cyclo*hexylimino*-3 : 5-*dihydrophenazine*.—2-*p*-Chloroanilino-5-*p*-chlorophenyl-3 : 5-dihydro-3-iminophenazine hydrochloride (0·2 g.) was heated under reflux with *cyclo*hexylamine (15 c.c.) for 30 min. The product (0·15 g.), purified chromatographically, was identical with that obtained by catalytic hydrogenation of 5 : 1′-di-*p*-chlorophenyl*cyclo*hexane*spiro*-2′-glyoxalino(5′ : 4′-2 : 3)phenazine.

*Recyclisation of Compound* (III; R = Ph, R‴ = Pr$^i$) *to the Glyoxalinophenazine* (I; R = Ph, R′ = R″ = Me).—The compound (III) (0·5 g.), concentrated hydrochloric acid (0·25 c.c.), and nitrobenzene (25 c.c.) were heated under reflux for 20 min. The cooled solution was poured into ether and the precipitated hydrochloride converted into the base which was purified chromatographically; this had m. p. and mixed m. p. 230—232° (yield, 0·07 g.). The compound in concentrated sulphuric acid is rose-red, unchanged on dilution.

The authors are grateful to J. R. Geigy, S.A., Basle, Switzerland, for financial aid.

LABORATORIES OF THE MEDICAL RESEARCH COUNCIL OF IRELAND,
TRINITY COLLEGE, DUBLIN. [*Received, September 24th*, 1957.]

---

## 167. *Electrolytic Reduction of Some αβ-Unsaturated Steroid Ketones.*

By PETER BLADON, J. W. CORNFORTH, and (MRS.) R. H. JAEGER.

Electrolytic reduction of cholest-4-en-3-one leads to the known "cholestenone pinacol," which is shown to be di-(3β-hydroxycholest-4-en-3α-yl). Reduction of 7-oxocholest-5-en-3β-yl acetate gives a thermally unstable pinacol, the stereochemistry of which is discussed; reduction of 20-oxopregna-5 : 16-dien-3β-yl acetate gives a stereoisomeric mixture of disteroid diketones coupled at the 16-position.

IN extending work [1] on the antituberculosis effect of polyethylene ethers, we required compounds of molecular weight 600—1000, containing one or more reactive hydroxyl groups capable of polycondensation with ethylene oxide. Disteroids (compounds containing two linked steroid nuclei) seemed able to fulfil these and certain other requirements (*e.g.*, polycyclic rather than long-chain structure; ease of preparation), and this paper describes an exploration of several compounds of this class.

[1] Cornforth, D'Arcy-Hart, Nicholls, Rees, and Stock, *Nature*, 1951, **168**, 150; *Brit. J. Pharmacol.*, 1955, **10**, 73.

XUM

Windaus [2] reduced cholest-4-en-3-one with sodium amalgam in alcoholic acetic acid and obtained a high-melting product of high molecular weight. Butenandt and Poschmann,[3] and Squire,[4] later showed that it was the pinacol (I) derived from cholestenone. The configuration of the hydroxyl groups was not determined.

The preparation of cholestenone pinacol by Squire's method was inconvenient on a large scale, because of the large amounts of sodium amalgam needed. We turned to the electrolytic reduction of cholestenone with mercury as cathode and ethanolic sodium acetate as electrolyte. It was expected that the Kolbe reaction leading to ethane and carbon dioxide would take place at the carbon rod anodes, and so no diaphragm was used to separate the anodes from the cathode (cf. Swann [5]). Under controlled conditions satisfactory yields of the pinacol were obtained. Under acid conditions at higher temperatures di(cholesta-3 : 5-dien-3-yl) was formed (cf. the formation of a similar compound by polarographic reduction of cortisone [6]).

We next sought to introduce the necessary reactive hydroxyl groups *via* an intermediate epoxide. The pinacol (I) rapidly consumed 2 mols. of perbenzoic acid, giving the expected diepoxide (II). Both epoxide rings in this compound have the β-configuration, since treatment with lead tetra-acetate gave 4β : 5β-epoxycholestanone [7] (III) in at least 64% yield.

An attempt to open the epoxide rings in (II) by treatment with aqueous perchloric acid in tetrahydrofuran yielded, not the expected hexahydric alcohol, but a compound (A) isomeric with the diepoxide. This is formulated as (IV) for the following reasons. Treatment with chromium trioxide in pyridine gave an amorphous diketone (B) (formulated as V), the infrared spectrum of which showed no absorption due to hydroxyl groups, and a single carbonyl peak at 1773 cm.$^{-1}$. Reduction of the ketone with lithium aluminium hydride regenerated the alcohol (A). Hence the hydroxyl groups in (A) must be secondary. The alternative structures (VI) and (VII) are excluded since carbonyl groups in 2-oxa*cyclo*butanones are known [8,9] to have absorption maxima at 1800—1820 cm.$^{-1}$. On the other hand 3-oxa*cyclo*pentanones such as (V) have absorption maxima at lower frequencies [9,10] (1748 and 1780 cm.$^{-1}$). The structure (IV), with ten fused rings, explains the remarkable insolubility and the thermal stability of the compound (A). It does not melt under 400°, and sublimes *in vacuo* at 350°. The hydroxyl groups in compound (A) are hindered: they could not be acetylated or toluene-*p*-sulphonylated in pyridine solution, nor could reaction with ethylene oxide be induced.

The isomerisation of cholestenone pinacol oxide (II) is envisaged as proceeding by the attack of the 3′-hydroxyl group on the rear (α) side of $C_{(5)}$, with simultaneous opening of the protonated 4β : 5β-epoxide ring, to form a 4β-hydroxyl group and a 3′β : 5α-epoxide ring; similar events occur in both halves of the molecule. It follows that the hydroxyl groups in cholestenone pinacol oxide, and in the pinacol itself, must be β-oriented; neither of the other arrangements (αα′; αβ′) permits the formation of a compound with the properties of (IV). The pinacol derived from androst-4-en-3-one [11] presumably has a similar structure.

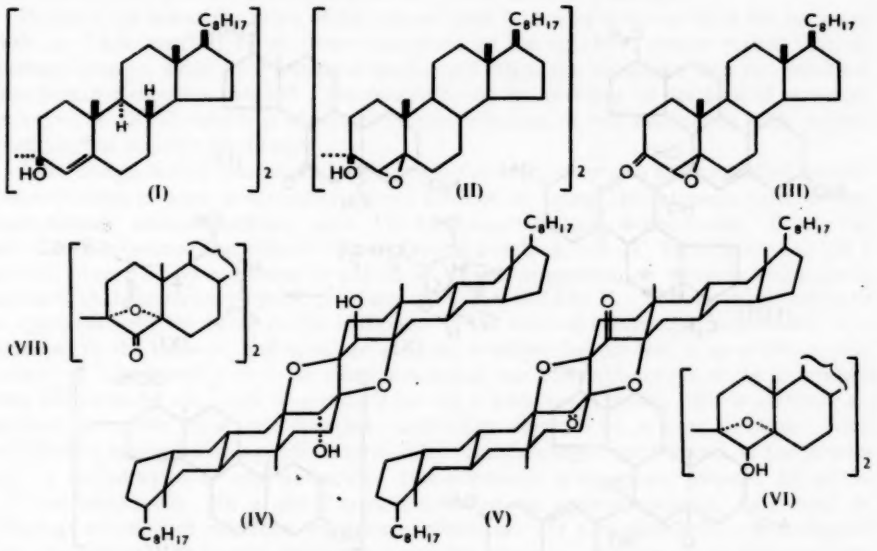
Similar electrolytic reduction was applied to 7-oxocholesteryl acetate. The crude product was chromatographed, three principal fractions being obtained: a mixture of 7-oxocholesteryl and 7-oxocholestanyl acetate; a solid (D), formulated as the pinacol (VIII);

[2] Windaus, *Ber.*, 1906, **39**, 521.
[3] Butenandt and Poschmann, *Ber.*, 1940, **73**, 893.
[4] Squire, *J. Amer. Chem. Soc.*, 1951, **73**, 2587.
[5] Swann, "Electrolytic Reactions," in "Technique of Organic Chemistry," ed. Weissberger, Interscience Publ. Inc., New York, 1948, Vol. II, p. 152.
[6] Kabasakallian and McGlotten, *J. Amer. Chem. Soc.*, 1956, **78**, 5032.
[7] Plattner, Heusser, and Kulkarni, *Helv. Chim. Acta*, 1948, **31**, 1822.
[8] Muir, Hoey, and Lester, *J. Amer. Chem. Soc.*, 1955, **77**, 4430.
[9] Hirschmann, Bailey, Poos, Walker, and Chemerda, *ibid.*, 1956, **78**, 4814.
[10] Allen and Bernstein, *ibid.*, p. 3223.
[11] Butenandt, Poschmann, Failer, Schiedt, and Biekert, *Annalen*, 1951, **575**, 123.

XUM

and a monomeric steroid, formulated as 3β-acetoxy-5ξ-hydroxycholestan-7-one (IX) since alkaline hydrolysis converted it into cholesta-3 : 5-dien-7-one.

The solid (D) was undoubtedly a pinacol, for it was cleaved smoothly by lead tetra-acetate to 7-oxocholesteryl acetate in 75% yield. The low melting point (149°) and low results in the Rast molecular-weight determination were puzzling until it was recognised




that the compound was decomposed on melting to an equimolecular mixture of 7-oxocholesteryl and 7-oxocholestanyl acetate. The melting point of the pinacol is in fact the melting point of the mixture, and the infrared and ultraviolet spectra of the melt were as expected. Both components were isolated from the cooled melt by chromatography over alumina.

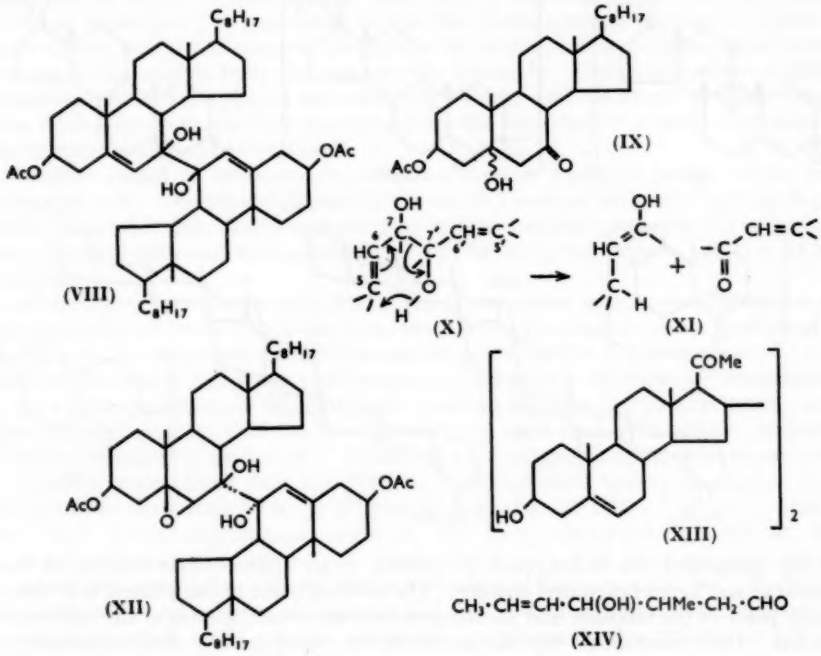
The pinacol (D) reacted rapidly with 1 mol. of perbenzoic acid, to give as the main product a monoepoxide. Further reaction was much slower and led to a compound which was presumably the diepoxide. Both products had high melting points, and the molecular weight found for the monoepoxide was in the range expected for a dimeric steroid.

Three structures are theoretically possible for the pinacol; in these, the tertiary hydroxyl groups are respectively 7α : 7′α, 7β : 7′β, and 7α : 7′β. Only the 7α-OH : 7′α-OH structure can be made on molecular (Catalin) models without severe distortion caused by interference between the two steroid nuclei, and rotation about the 7 : 7′ bond does not seem possible with any structure. The simplest explanation of the perbenzoic acid oxidation is that the two double bonds are non-equivalent; this is only true of the 7α-OH : 7′β-OH structure. Moreover, this structure allows a plausible explanation of the fission on pyrolysis, which can be seen as a concerted reaction with a cyclic transition state (X ⟶ XI) of a type which has been postulated in the thermal decomposition of β-oxo-acids[12] and βγ-unsaturated acids[13] and in the pyrolysis of certain esters yielding olefins.[14] The relative thermal stability of the monoepoxide can then be understood if the 5 : 6-double bond participating in this transition state is the first to be oxidised (XII).

[12] Westheimer and Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 3283.
[13] Arnold, Elmer, and Dodson, *ibid.*, 1950, **72**, 4359; Barton and Brooks, *J.*, 1951, 257.
[14] Cram, "Olefin Forming Elimination Reactions," in "Steric Effects in Organic Chemistry," ed. Newman, Wiley, New York, 1956, p. 305.

XUM

However, reluctance to form a diepoxide does not necessarily mean non-equivalence of the two double bonds in such crowded structures as these pinacols. Three steric factors might operate against introduction of a second oxygen atom: (i) the first oxygen atom directly obstructs introduction of the second, (ii) the change in conformation at position 7, consequent upon the first epoxidation, increases steric shielding of the second double bond, (iii) the second epoxidation is resisted because the resulting change in conformation would




cause excessive steric compression. Though it is hard to assess the relative importance of such factors, they suggest that the symmetrical 7α-OH : 7′α-OH structure, which is the least strained of the three, cannot be excluded by the evidence of perbenzoic acid oxidation. The thermal fission need not, of course, be an intramolecular process, as in (X ⟶ XI); the strained 7 : 7′-bond might suffer a heterolysis which would be facilitated by both double bonds. The stereochemistry of this pinacol at positions 7 and 7′ remains undetermined.

Attempts to obtain a pinacol by electrolytic reduction of 3β-acetoxypregna-5 : 16-dien-20-one, in the apparatus used with cholestenone and 7-oxocholesteryl acetate, failed to yield a crystalline product. Accordingly the process was modified. The cell consisted of a mercury cathod of limited area (4 cm.²), a carbon rod anode, and an electrolyte of sodium acetate in methanolic acetic acid. The concentration of the steroid was higher than in the previous experiments, and the solution was allowed to reflux. The crude product afforded a solid, some of which had separated during the electrolysis. It was found to be a mixture which could not be separated into pure components by chromatography or crystallisation. The absence of a hydroxyl absorption band in its infrared spectrum showed that it did not contain a pinacol, and the peaks in the carbonyl region indicated that both ketone and acetate groups were present.

The corresponding mixture of alcohols obtained on saponification was separated into

two pure components by crystallisation. These were characterised as acetates and benzoates, and are regarded as two isomeric forms of di-(3β-hydroxy-20-oxopregn-5-en-16-yl) (XIII). They are referred to as " isomer I " and " isomer II ". There appears to be no stereochemical reason why a pinacol should not have been formed in this reduction, and the coupling at the 16-position must be attributed to its high reactivity compared with that of the 5-position in cholestenone and 7-oxocholesteryl acetate.

Bands in the infrared spectra of the acetate (and benzoate) of isomer II in the region of 3500 cm.$^{-1}$ are ascribed to overtone absorption of the carbonyl groups rather than to hydroxyl groups, since they remained unchanged when the substance was recrystallised from dioxan–deuterium oxide.[15] The possibility of the presence of the type of structure analogous to (XIV), which is obtained by the reduction of crotonaldehyde with sodium amalgam,[16] is thereby eliminated.

After completion of this work, Lund [17] reported experiments on the controlled electrolytic reduction of some unsaturated steroid ketones, including cholestenone, testosterone, progesterone, androstenedione, and 17β-hydroxyandrosta-1 : 4-dien-3-one. From the last-named substance two different pinacols were obtained, one (*X*) by reduction at pH 5 and the other (*Y*) by reduction at pH 12·5. It was suggested, on grounds which merit criticism, that the tertiary hydroxyl groups are α in *X* and β in *Y*. The steroid is presumed to approach with its α-face to the cathode. If the carbonyl oxygen is protonated, it is attracted to the cathode, and when an electron is added the product is an allylic radical having an α-hydroxyl group; in alkaline solution the carbonyl-oxygen atom is repelled from the cathode and leads to a radical having a β-hydroxyl group. These radicals are assumed to retain these configurations until they dimerise by a slow reaction. Such retention of configuration appears improbable. Another argument is based on the greater ease of dehydration of one isomeride; this argument gratuitously assumes an initial $S_N2'$ rearrangement. In a third argument based on optical rotation, differences in *molecular* rotation of reference substances, which are not 1 : 4-dien-3-ols, are compared with the difference in *specific* rotation between the pinacols. It seems to us that configurations cannot yet be confidently assigned to these two isomerides. Configurations for the other pinacols were not suggested.

## Experimental

Unless otherwise indicated, m. p.s were determined in evacuated capillaries; on a Kofler block [m. p.s marked (K)] the less fusible compounds melted neither sharply nor reproducibly. Optical rotations were determined for $CHCl_3$ solutions, ultraviolet spectra were determined for EtOH solutions (unless stated otherwise). Deactivated alumina was prepared by shaking alumina (Peter Spence, Type H) in light petroleum with 10% aqueous acetic acid (5 c.c. per 100 g.). Extracts were normally dried over anhydrous sodium sulphate.

*Di-(3β-dihydroxycholest-4-en-3α-yl)* (I).—(a) Reduction of cholestenone with sodium amalgam by Squire's method [4] gave the pinacol in 45% yield as needles (from benzene–acetone), m. p. 225—227°, $[\alpha]_D$ +92° (*c* 1·05). Squire records m. p. 200—205°, $[\alpha]_D$ +110°; Butenandt records [3] m. p. 200°, $[\alpha]_D$ +103°. (b) *Electrolytic reduction of cholestenone.* The apparatus shown in Fig. 1 was employed. In the 1 l. beaker were placed sodium acetate trihydrate (20 g.), cholest-4-en-3-one (12 g.), ethanol (750 c.c.), and mercury (900 g.). The mixture was electrolysed for 1 hr. A potential between 160 and 190 v was needed to maintain a current of approximately 3 amps. The temperature was kept between 20° and 30° by addition of solid carbon dioxide to the acetone bath surrounding the beaker, and by adjustments of the current. The end of the reduction was marked by the sharp increase of the resistance of the cell (due to the withdrawal of sodium ions as sodium hydrogen

[15] Jones and Sandorfy, " The Application of Infrared and Raman Spectrometry to the Elucidation of Molecular Structure," in " Technique of Organic Chemistry," ed. Weissberger, Interscience Publ. Inc., New York, 1956, Vol. IX, p. 425.
[16] Nahum, *Compt. rend.*, 1956, **243**, 849.
[17] Lund, *Acta Chem. Scand.*, 1957, **11**, 283.

carbonate which is precipitated). The reaction mixture was poured into water (1·5 l.), and the solid coagulated by stirring, collected, roughly dried, and dissolved in benzene. Any water present was separated or removed with sodium sulphate. The solution was filtered (to remove traces of mercury) and concentrated. Addition of acetone yielded di-(3β-hydroxy-cholest-4-en-3α-yl) as needles (5·1—6·1 g., 42—51%), m. p. 227—230°, $[\alpha]_D$ +91° (*c* 0·84), $\nu_{max.}$ (KCl) 3320 (OH), 1665 cm.$^{-1}$ (–CH=C–).

Electrolytic reduction of cholestenone (4 g.) in propan-1-ol (150 c.c.) and glacial acetic acid (150 c.c.) containing sodium acetate trihydrate (15 g.) for 3 hr. at 60—70° (ice-cooling), gave di(cholesta-3 : 5-dien-3-yl) (40%), as pale yellow crystals (from chloroform), m. p. 365—370° (decomp.), $[\alpha]_D$ −193° (*c* 0·129) (Found: C, 88·2; H, 11·5. Calc. for $C_{54}H_{86}$: C, 88·2; H, 11·8%). $\lambda_{max.}$ (in $CHCl_3$) 298, 311, and 326 mμ (ε 32,000, 41,540, 30,000). Squire [4] records m. p. 243—247°, $[\alpha]_D$ −260°, $\lambda_{max.}$ (in $CHCl_3$) 298, 312, and 323 mμ (ε 48,000, 63,100, 47,000).

*Di*-(3β-*hydroxy*-4β : 5β-*epoxycholestan*-3α-*yl*) (II).—Cholestenone pinacol (I) (8 g.) in chloroform (140 c.c.) was treated with 0·45M-perbenzoic acid in benzene (45 c.c., 2·4 mols.), and kept overnight at room temperature. Water and aqueous potassium hydrogen carbonate were added, and the chloroform layer was separated, washed with water, dried, and evaporated to

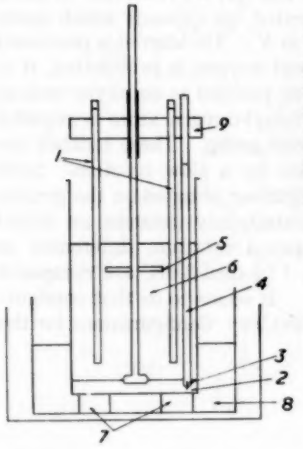



FIG. 1.

1, Carbon rod anodes (four).
2, Mercury cathode.
3, Platinum wire connection.
4, Mercury connection.
5, Stirrer.
6, Electrolyte.
7, Cork spacers.
8, Acetone–solid carbon dioxide freezing mixture.
9, Cork support for electrodes and stirrer.

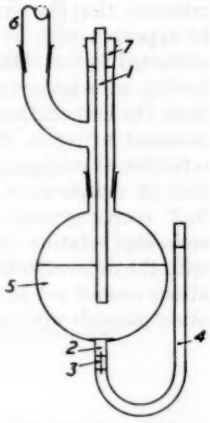



FIG. 2.

1, Carbon rod anode.
2, Mercury cathode.
3, Platinum wire connection.
4, Mercury connection.
5, Electrolyte.
6, Reflux condenser.
7, Rubber stopper.

small bulk. Addition of acetone yielded crystals, m. p. 315° (7·9 g.). Recrystallisation of a portion from chloroform–acetone gave needles of *di*-(3β-*hydroxy*-4β : 5β-*epoxycholestan*-3α-*yl*), m. p. 315°, $[\alpha]_D$ +0·2° (*c* 0·83) (Found: C, 81·1; H, 11·1. $C_{54}H_{90}O_4$ requires C, 80·7; H, 11·2%). $\nu_{max.}$ (in KCl) 3500 cm.$^{-1}$ (OH).

With excess of perbenzoic acid the first 2 mols. were consumed rapidly (15 min.), and then a further slow uptake occurred during 24 hr., approaching 6 mols. Material isolated after this time had m. p. 305°, $[\alpha]_D$ +0·2° (*c* 1·16) (Found: C, 79·7; H, 11·2%). It gave a good yield of pure product in the rearrangement reaction (see below).

*Treatment of Cholestenone Pinacol Diepoxide with Lead Tetra-acetate.*—The diepoxide (500 mg.) in dry benzene (10 c.c.) was treated with lead tetra-acetate (600 mg.) in dry benzene (25 c.c.) and set aside for 1 hr. Ethylene glycol (2 c.c.) was added, followed by dilute acetic acid. The product was isolated by ether-extraction, and the extracts were washed with water and dried. Evaporation of the extracts gave an oil (494 mg.) which solidified with methanol. Two recrystallisations from acetone–methanol gave 4β : 5β-epoxycholestan-3-one (III) (321 mg.), as needles, m. p. 119—121° (K), $[\alpha]_D$ +131° (*c* 1·01) (Found: C, 81·1; H, 11·2. Calc. for $C_{27}H_{44}O_2$: C, 80·95; H, 11·1%). The infrared spectrum was identical with that of an authentic specimen prepared by the method of Plattner *et al.*,[7] and the m. p. of the mixture of material from both sources was not depressed.

*Di*-(3β : 5′α-*epoxy*-4β-*hydroxycholestan*-3α-*yl*) (IV).—Cholestenone pinacol diepoxide (4 g.) in tetrahydrofuran (200 c.c.) was treated with 60% aqueous perchloric acid (10 c.c.) and kept

overnight at room temperature. Addition of water precipitated a solid, which was collected, washed with water, resuspended in water containing sodium hydroxide, collected, washed with water, and dried *in vacuo* (yield 4 g.; m. p. >390°). Recrystallisation from tetrahydrofuran–acetone afforded pure *di*-(3β : 5′α-*epoxy*-4β-*hydroxycholestan*-3α-*yl*), m. p. >400°, $[\alpha]_D$ +16·7° (*c* 1·55 in pyridine) (Found: C, 80·7; H, 11·0. $C_{54}H_{90}O_4$ requires C, 80·7; H, 11·2%), $\nu_{max.}$ (in KCl) 3590 and 3450 cm.$^{-1}$ (OH). This compound sublimes unchanged at 340°/$10^{-5}$ mm.

*Di*-(3β : 5′α-*epoxy*-4-*oxocholestan*-3α-*yl*) (V).—Di-(3β : 5′α-epoxy-4β-hydroxycholestan-3α-yl) (500 mg.) in pyridine (35 c.c.) was added to a solution of chromium trioxide (2·0 g.) in pyridine (50 c.c.). Next day, excess of dilute hydrochloric acid was added, followed by solid sodium sulphite. After 1 hour's stirring the precipitated solid was collected and dried *in vacuo*. The light grey amorphous solid, m. p. 330°, $[\alpha]_D$ −91·7° (*c* 1·25), did not crystallise from the usual solvents. A hot solution in dimethylformamide formed a stiff gel on cooling. A sample purified by pouring a boiling solution in dimethylformamide into boiling water became granular on drying. The *diepoxide* had $[\alpha]_D$ −90·4° (*c* 0·90) (Found: C, 81·4; H, 10·65. $C_{54}H_{86}O_4$ requires C, 81·2; H, 10·85%), $\nu_{max.}$ (in $CHCl_3$) 1773 cm.$^{-1}$ (C=O), no hydroxyl band.

The ketone (V) (250 mg.) in tetrahydrofuran (25 c.c.) was refluxed with lithium aluminium hydride (500 mg.) for 4 hr. Decomposition of excess of reagent with acetone, followed by hydrochloric acid, precipitated a white solid (237 mg.). This was dissolved in tetrahydrofuran and the solution filtered through kieselguhr and evaporated to small bulk. Addition of acetone precipitated di-(3β : 5′α-epoxy-4β-hydroxycholestan-3α-yl) (167 mg.), m. p. >380°, having an infrared spectrum identical with that of authentic material.

*Electrolytic Reduction of 7-Oxocholesteryl Acetate.*—The apparatus was similar to that used for the electrolysis of cholestenone. 7-Oxocholesteryl acetate (6 g.) and sodium acetate trihydrate (15 g.) in ethanol (600 c.c.) were electrolysed for 3 hr. A potential of 140 v resulted in a current of 4 amp. when the temperature was kept at 40°. Acetic acid (25 c.c.) was added during the reduction, completion of which was marked by a drop in current. The reaction mixture was poured into water (2000 c.c.) and the precipitated solid collected, washed with water, and roughly dried *in vacuo*. It was dissolved in dichloromethane; the solution was dried and evaporated. The residue was dissolved in 4 : 1 light petroleum–benzene and chromatographed on deactivated alumina (600 g.). Fractions of 110 c.c. were collected and evaporated. Fractions 1—15 (4 : 1 to 1 : 1 light petroleum–benzene) yielded oils (0·293 g.). Fractions 16—69 (1 : 1 light petroleum–benzene to benzene) yielded crystals (C) (3·688 g.). Fractions 70—79 (9 : 1 benzene–ether) gave a solid (D) (1·232 g.). Fractions 80—88 (9 : 1 benzene–ether to ether) yielded oils (0·149 g.). Fractions 89—109 (ether) yielded solid (E) (0·485 g.). Finally elution with 9 : 1 ether–methanol (fractions 110—119) gave only oily material.

The solid (C) had the characteristics of a mixture of 7-oxocholesteryl and 7-oxocholestanyl acetate.

Solid (D), recrystallised from dichloromethane–acetone, had m. p. 146—149° (K) (640 mg.). Further recrystallisation afforded pure 3β-*acetoxy*-7-(3β-*acetoxy*-7-*hydroxycholest*-5-*en*-7-*yl*)-*cholest*-5-*en*-7-*ol* (*7-oxocholesteryl acetate pinacol*) (VIII), m. p. 149—152° (K), $[\alpha]_D$ −57·8° (*c* 1·05) (Found: C, 78·7, 78·4; H, 10·8, 10·5%; *M*, 343, 360. $C_{58}H_{94}O_6$ requires C, 78·5; H, 10·7%; *M*, 887), $\nu_{max.}$ (in KCl) 3510 and 3420 (OH), 1730 and 1240 cm.$^{-1}$ (OAc), $\nu_{max.}$ (in $CHCl_3$) 3510 (OH), 1724 cm.$^{-1}$ (OAc). A sample recrystallised from tetrahydrofuran by addition of deuterium oxide (99·2%) had $\nu_{max.}$ (in $CHCl_3$) 3510 (OH), 2654 (OD), and 1724 cm.$^{-1}$ (OAc).

Solid (E) recrystallised from dichloromethane–ether gave 3-*acetoxy*-5ξ-*hydroxycholestan*-7-*one* (IX) (135 mg.), m. p. 225—226° (K), $[\alpha]_D$ −44° (*c* 0·60) (Found: C, 75·6, 75·4; H, 10·7, 10·5; M, 474. $C_{29}H_{48}O_4$ requires C, 75·6; H, 10·5%; *M*, 460), $\nu_{max.}$ (in KCl) 3360 (OH), 1728 and 1250 (OAc), and 1703 cm.$^{-1}$ (C=O).

*Treatment of 7-Oxocholesteryl Acetate Pinacol with Lead Tetra-acetate.*—The pinacol (200 mg.) in dry benzene (6 c.c.) was treated with lead tetra-acetate (300 mg.) in dry benzene (10 c.c.). Immediate precipitation of lead diacetate occurred. After 1 hr. ethylene glycol (1 c.c.) was added and, after a further 0·5 hr. of intermittent shaking, the product was isolated by addition of dilute acetic acid and extraction with ether. Evaporation of the dried extracts yielded a solid residue (197 mg.). Crystallisation from acetone–methanol gave platelets of 7-oxocholesteryl acetate (151 mg.), m. p. and mixed m. p. 159—161° (K) (with a change of crystalline form at 147—150°; sometimes with melting and resolidifying), $[\alpha]_D$ −101° (*c* 1·30). This material had an infrared spectrum identical with that of authentic material.

*Thermal Decomposition of 7-Oxocholesteryl Acetate Pinacol.*—Small samples of the pinacol

XUM

after melting and cooling showed $\lambda_{max.}$ 235 mμ (ε 6455), $\nu_{max.}$ (in $CCl_4$) 1735, 1707, 1675, and 1631 cm.$^{-1}$.

The pinacol (200 mg.) was heated at 160—170° for 5 min. in nitrogen. The product solidified on cooling and was chromatographed in light petroleum on deactivated alumina (100 g.). Elution with light petroleum–benzene (3 : 2 to 1 : 1) (450 c.c.) gave traces of oily material. Elution with mixtures containing more benzene (1 : 1 to 1 : 4) and finally pure benzene (450 c.c.) gave 5 solid fractions. The first of these (46 mg.), plates, m. p. 144—150° (K), had $\nu_{max.}$ (in $CCl_4$) 1731, 1708 cm.$^{-1}$.

Recrystallisation from methanol gave 7-oxocholestanyl acetate (29 mg.) as plates, m. p. and mixed m. p. 150—152° (K), $[\alpha]_D$ −39·5° (*c* 0·57), $\nu_{max.}$ (in KCl) 1725 (OAc), 1700 cm.$^{-1}$ (C=O). An authentic specimen prepared by hydrogenation of 7-oxocholesteryl acetate (Wintersteiner and Moore [18]) had m. p. 149—151° (K), $[\alpha]_D$ −35·5° (*c* 1·25), and an identical infrared spectrum. The last two fractions (total 45 mg.) formed prisms, m. p. 158—163° (K) (change of form at 150°), and had $\nu_{max.}$ (in $CCl_4$) 1732, 1675, and 1630 cm.$^{-1}$. Recrystallisation from acetone–methanol gave prisms of 7-oxocholesteryl acetate (31 mg.), m. p. and mixed m. p. 161—163° (K) (with a change of form at 149—152°), $[\alpha]_D$ −103° (*c* 0·61), $\nu_{max.}$ (in KCl) 1727 (OAc), 1667 and 1630 cm.$^{-1}$ (C=CH–C=O). Authentic material had m. p. 158—160° (K), $[\alpha]_D$ −99° (*c* 1·29), $\lambda_{max.}$ 225 mμ (ε 12,170) and an identical infrared spectrum. The two intermediate fractions had infrared spectra similar to that of the mixture before chromatography, so were mixtures of 7-oxocholesteryl and 7-oxocholestanyl acetate. The total amount eluted from the column was 199 mg.

*Treatment of 7-Oxocholesteryl Acetate Pinacol with Perbenzoic Acid.*—The pinacol in dichloromethane, treated with excess of perbenzoic acid in benzene, consumed 1 mol. within 15 min. Thereafter, reaction was slower and after 24 hr. 1·7 mol. had been consumed. The product (m. p. 265—277°) isolated at this stage was identical with the second material described below.

To the pinacol (250 mg.) in dichloromethane (5 c.c.) was added 0·44M-perbenzoic acid (0·71 c.c., 1·1 mol.), and the mixture was kept until only a trace of per-acid was left (3 hr.). The product was isolated by adding ether and washing the whole with dilute potassium hydroxide solution. Evaporation of the dried ethereal phase yielded an oil (268 mg.) which rapidly solidified. Recrystallisation from dichloromethane–acetone afforded needles of the *monoepoxide* (XII), m. p. 230—233°, $[\alpha]_D$ −34·9° (*c* 1·10) (Found: C, 76·9; H, 10·5%; *M*, 708. $C_{58}H_{94}O_7$ requires C, 77·1; H, 10·5%; *M*, 902), $\nu_{max.}$ (in KCl) 3520 and 3420 (OH), 1735 and 1243 cm.$^{-1}$ (OAc).

When the pinacol (500 mg.) in dichloromethane (5 c.c.) was kept with 0·44M-perbenzoic acid (1·409 c.c., 1·1 mol.) for 24 hr., the crude product (525 mg.), treated with ether, yielded crystals, m. p. 250—270° (51 mg.). Recrystallisation from dichloromethane–acetone afforded a *diepoxide*, m. p. 265—277° (decomp.), $[\alpha]_D$ −24·7° (*c* 0·41) (Found: C, 75·5; H, 10·3. $C_{58}H_{94}O_8$ requires C, 75·8; H, 10·3%), $\nu_{max.}$ (in KCl) 3410 (OH), 1730, and 1245 cm.$^{-1}$ (OAc.) The ethereal mother-liquors, on concentration and addition of acetone, gave needles, m. p. 235—237° (122 mg.). Recrystallisation from dichloromethane–acetone gave the monoepoxide as needles, m. p. 229—231°, $[\alpha]_D$ −35·2° (*c* 0·89) (Found: C, 77·2; H, 10·5%), whose infrared spectrum was identical with that of the material described above.

*Alkali Treatment of 3β-Acetoxy-5ξ-hydroxycholestan-7-one.*—The ketone (45 mg.) was refluxed with 50% w/v aqueous potassium hydroxide (1 c.c.) in tetrahydrofuran (1 c.c.) and methanol (6 c.c.) for 1 hr. Working up with water and ether and chromatography of the crude oil (43 mg.) on deactivated alumina (4 g.) yielded a solid (35 mg.). Crystallisation from methanol gave cholesta-3 : 5-dien-7-one, m. p. 110—113° (K), identical with a specimen prepared by alkaline hydrolysis of 7-oxocholesteryl acetate.

*Electrolytic Reduction of 3β-Acetoxypregna-5 : 16-dien-20-one.*—The apparatus is shown in Fig. 2. In the flask were placed the mercury cathode (5 c.c.), methanol (300 c.c.), acetic acid (7·5 c.c.), and sodium acetate trihydrate (7·5 g.). The electrolysis was started, and when the contents of the flask had begun to boil, 3β-acetoxypregna-5 : 16-dien-20-one (15 g.) and methanol (50 c.c.) were added. The electrolysis was resumed, whereupon the steroid rapidly dissolved. A potential of 220 v across the cell produced a current of about 1 amp. The current was unsteady because of the boiling of the solution at the mercury surface. After about 4 hr. when 3·5 ampère-hours had passed through the cell, the contents were added to water, and the

[18] Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1503.

XUM

precipitated material isolated by extraction with ether and dichloromethane in the usual way. Evaporation of the extracts left a syrup which was treated with methanol to give a solid (4·7—5·4 g.), m. p. 260—290°. The combined solid products (13·8 g.) from several experiments (39 g. of starting material) were recrystallised once from dichloromethane–acetone, to yield a solid (F) (9·64 g.), m. p. 270—280°, $[\alpha]_D$ −16·7° (*c* 0·92), $\nu_{max.}$ (in Nujol) 1735 and 1242 (OAc), 1709 cm.$^{-1}$ (C=O), no hydroxyl peak. From the mother-liquors a second crop (G) was obtained (2·1 g.), m. p. 250—300°.

*Saponification of the solid* (G). The solid (G) (2·1 g.) in 2-methoxyethanol (70 c.c.) was refluxed with 50% w/v aqueous potassium hydroxide solution for 1·5 hr. The mixture was poured into water and acidified with dilute hydrochloric acid. The precipitated solid was filtered off and dried (1·73 g.). One recrystallisation from methanol gave crystals (1·2 g.), m. p. 304—316°. Recrystallisation from 2-methoxyethanol gave needles of *di*-(3β-*hydroxy*-20-*oxopregn*-5-*en*-16-*yl*), *isomer I* (XIII), m. p. 325—329°, $[\alpha]_D$ −80·8° (*c* 0·86) (Found: C, 79·6; H, 9·95. $C_{42}H_{62}O_4$ requires C, 79·95; H, 9·9%), $\nu_{max.}$ (in Nujol) 3431 (OH), 1690 cm.$^{-1}$ (C=O). Acetylation with acetic anhydride and pyridine at room temperature gave *di*-(3β-*acetoxy*-20-*oxopregn*-5-*en*-16-*yl*), *isomer I*, needles (from dichloromethane–acetone), double m. p. 293—296° and 302—303°, $[\alpha]_D$ −80° (*c* 0·63) (Found: C, 77·6; H, 9·6. $C_{46}H_{66}O_6$ requires C, 77·3; H, 9·3%), $\nu_{max.}$ (in Nujol) 1724 and 1242 (OAc), 1706 cm.$^{-1}$ (C=O). Benzoylation with benzoyl chloride and pyridine gave *di*-(3β-*benzoyloxy*-20-*oxopregn*-5-*en*-16-*yl*), *isomer I*, m. p. 352—355° (decomp.) (from dichloromethane), $[\alpha]_D$ −30·4° (*c* 0·69) (Found: C, 80·2; H, 8·7. $C_{56}H_{70}O_6$ requires C, 80·1; H, 8·4%). $\nu_{max.}$ (in Nujol) 1718 (C=O and OBz), 1289 and 1277 cm.$^{-1}$ (OBz).

*Saponification of solid* (F). The solid (F) (6·0 g.) in 2-methoxyethanol (150 c.c.) was refluxed for 2 hr. with potassium hydroxide (10 g.) in water (15 c.c.). The mixture was poured into water and acidified with dilute hydrochloric acid. The solid product was collected and dried *in vacuo*. The solid was dissolved in boiling 2-methoxyethanol, which was concentrated after filtration to small bulk (125 c.c.) and cooled. The first crop of crystals was collected, washed with ether, and dried, to give di-(3β-hydroxy-20-oxopregn-5-en-16-yl), isomer I (933 mg.), m. p. 320—325°, $[\alpha]_D$ −79° (*c* 0·75). The infrared spectrum was identical with that of the material described earlier.

The mother-liquors were concentrated to small bulk (25 c.c.), giving a second crop (900 mg.), m. p. 255—260° (sintering at 200—220°), which was washed with methanol. Boiling of the methanolic filtrates caused the separation of a third crop, as needles (1715 mg.), m. p. 268—270° (sintering at 193—200°). This gave on recrystallisation from 2-methoxyethanol, *di*-(3β-*hydroxy*-20-*oxo*-*pregn*-5-*en*-16-*yl*), *isomer II* (XIII), m. p. 269—271°, $[\alpha]_D$ −9·0° (*c* 0·69), −8·20° (*c* 0·76), −8·2° (*c* 1·24) (three separate preparations) (Found: C, 77·95, 77·9; H, 10·3, 9·9%; *M*, 698. $C_{42}H_{62}O_4,H_2O$ requires C, 77·7; H, 9·9%; *M*, 649) (the water of crystallisation was not given up on drying at 130°/0·01 mm.), $\nu_{max.}$ (in Nujol) 3390 (OH), 1705 cm.$^{-1}$ (C=O). The *diacetate*, *isomer II*, prepared in the usual way and crystallised from dichloromethane–methanol, had m. p. 287—290° (depressed on admixture with the diacetate, isomer I), $[\alpha]_D$ −22·4° (*c* 1·15) (Found: C, 77·0; H, 9·5%; *M*, 623. $C_{46}H_{66}O_6$ requires C, 77·3; H, 9·3%; *M*, 715), $\nu_{max.}$ (in Nujol) 3262 (C=O overtone), 1740 and 1242 (OAc), and 1713 cm.$^{-1}$ (C=O), $\nu_{max.}$ (in $CHCl_3$) 3509 (C=O overtone), 1739 (OAc), and 1709 cm.$^{-1}$ (C=O). The infrared spectrum in chloroform was not changed by recrystallisation of the solid from dioxan–deuterium oxide (99·2%). The *dibenzoate*, *isomer II*, prepared in the usual way and crystallised from dichloromethane–acetone, had m. p. 346—348° (decomp.), $[\alpha]_D$ +18·6° (*c* 0·74) (Found: C, 80·0; H, 8·6. $C_{56}H_{70}O_6$ requires C, 80·1; H, 8·4%), $\nu_{max.}$ (in Nujol) 3335 (C=O overtone), 1715 (C=O and OBz), 1279 cm.$^{-1}$ (OBz).

We acknowledge with thanks a generous gift of dehydropregnenolone acetate from Dr. V. Petrow (British Drug Houses Ltd.). We also thank Mrs. J. Fair (Mill Hill) and Mr. W. McCorkindale (Glasgow) for microanalyses, Miss N. Caramando (Glasgow) for infrared spectra, and Mr. J. Grant (Mill Hill) for technical assistance.

National Institute for Medical Research, London, N.W.7.
The Royal College of Science and Technology,
Glasgow, C.1.

[*Received, October 2nd*, 1957.]

XUM

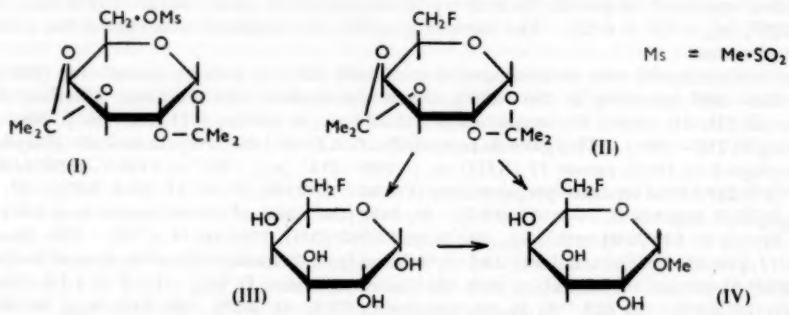
## 168. *Fluorocarbohydrates. Part I. The Synthesis of 6-Deoxy-6-fluoro-α-D-galactose and 5-Deoxy-5-fluoro-αβ-D-ribose.*

By N. F. Taylor and P. W. Kent.

Fluorinated monosaccharides have been synthesised by exchange reactions in ethanediol with anhydrous potassium fluoride and the appropriate primary methanesulphonyl esters. In methanol, halogenation is accompanied by the introduction of one *O*-methyl group into the product. The described deoxy-fluoro-sugars appear to behave normally towards sodium metaperiodate and are converted into the glycosides by methanolic hydrogen chloride.

The similarity in size and electronegativity of the fluorine atom and the hydroxyl group, coupled with their capacity to enter into hydrogen-bond formation, suggests the possibility of a new class of carbohydrates in which one or more of the hydroxyl groups have been replaced by fluorine. In 1941 Helferich and Gnüchtel [1] synthesised 6-deoxy-6-fluoro-α-D-glucopyranose by an exchange reaction between hydrated potassium fluoride and 3 : 5-*O*-benzylidene-6-*O*-methanesulphonyl-1 : 2-*O*-*iso*propylidene-D-glucofuranose. Two other routes have been reported for the introduction of fluorine into carbohydrates: (*a*) the action of anhydrous hydrogen fluoride on fully acetylated sugars, to give glucosyl fluorides; [2] and (*b*) total synthesis, as in the case of 2-deoxy-2-fluoro-DL-glyceraldehyde.[3]

We have now investigated the action of potassium fluoride on the sulphonyloxy-derivatives of D-galactose and D-ribose with the object of establishing a general method for the introduction of fluorine into extracyclic positions of carbohydrate molecules.




In contrast to 3 : 5-*O*-benzylidene-6-*O*-methanesulphonyl-1 : 2-*O*-*iso*propylidene-D-glucose, attempts to replace the methanesulphonyloxy-group by fluorine in 6-*O*-methanesulphonyl-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose (I) under Helferich and Gnüchtel's conditions (100° for 15 hr. in methanol) were unsuccessful. Exchange occurred however at 150°. A similar difference in reactivity of these two methanesulphonyl compounds towards iodide exchange is known.[4]

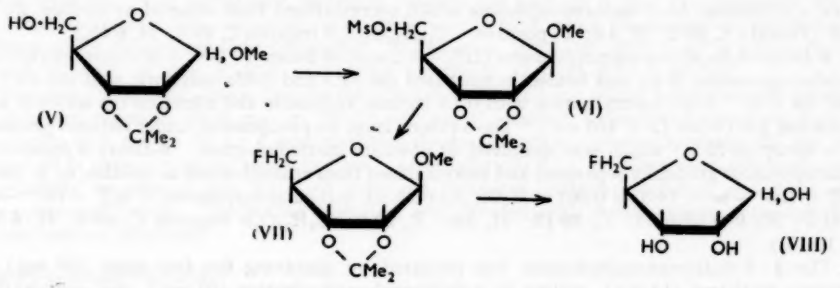
When the methanesulphonyl derivative (I) was heated with hydrated potassium fluoride in methanol at 150° for 17 hr. exchange occurred, the yield of potassium methanesulphonate being practically quantitative. A fluorine-containing product was obtained as a liquid [5] ($[\alpha]_D^{20}$ −64·5° in $CHCl_3$) which contained *O*-methyl groups (OMe, 7·3%). Acid hydrolysis of this product gave a crystalline reducing sugar containing one methoxyl

[1] Helferich and Gnüchtel, *Ber.*, 1941, **74**, 1035.
[2] Brauns, *J. Amer. Chem. Soc.*, 1923, **45**, 833, 2381; 1924, **46**, 1484; 1926, **48**, 2776; 1929, **51**, 1820.
[3] Taylor and Kent, *J.*, 1956, 2150.
[4] Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366; Foster, Overend, Stacey, and Wiggins, *J.*, 1949, 2542.
[5] Taylor and Kent, *Research*, 1956, **9**, 528.

group (OMe, 15·1%). On the basis of its mutarotation, $[\alpha]_D^{20}$ +129° ⟶ +53·5° (in $H_2O$), the free sugar was judged to be in the cyclic α-form. The nature of these compounds will be considered in a later paper.

In experiments to avoid this methylation we investigated the suitability of other solvents for potassium fluoride. Glycerol and ethanediol proved excellent solvents for both anhydrous and hydrated potassium fluoride. Exchange readily occurs when the ester (I) is refluxed for 75 min. with anhydrous potassium fluoride in ethanediol, giving 6-deoxy-6-fluoro-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactopyranose (II). Acid hydrolysis of this gave the crystalline free sugar (III) as the α-isomer, which contained no *O*-methyl group and gave a crystalline 2 : 5-dichlorophenylhydrazone. Methanolic hydrogen chloride converted either product (II) or (III) into the crystalline 6-deoxy-6-fluoro-α-D-galactopyranoside (IV). The glycoside readily consumed 2 mols. of sodium metaperiodate, and afforded the crystalline tri-*O*-methanesulphonate.

Analogous reactions were carried out with D-ribose. Methyl 2 : 3-*O*-*iso*propylidene-αβ-D-ribofuranoside (V) was converted into the crystalline ester (VI) which with anhydrous potassium fluoride in refluxing ethanediol gave the fluoride (VII), a mobile volatile liquid, in 60% yield in 1 hr. Acid hydrolysis gave 5-deoxy-5-fluoro-αβ-D-ribose (VIII) as a syrup which was chromatographically pure and was characterised as the crystalline 2 : 5-dichlorophenylhydrazone. As in the case of D-galactose, the exchange reaction in methanol gave a fluorine-containing derivative having one *O*-methyl group.




The advantages of ethanediol as a solvent are demonstrated in the case of 3 : 5-*O*-benzylidene-6-*O*-methanesulphonyl-1 : 2-*O*-*iso*propylidene-D-glucofuranose. This affords the 6-deoxy-6-fluoro-derivative (identical with that obtained under Helferich and Gnüchtel's conditions) in good yield when refluxed with anhydrous potassium fluoride in ethanediol for 2·5 min. When heated with 1% methanolic hydrogen chloride, 6-deoxy-6-fluoro-D-glucose [1] is converted into the corresponding methyl α-pyranoside which consumed 1·85 mols. of sodium metaperiodate.

It is notable that Helferich and Gnüchtel [1] did not observe anomalous methylation in their exchange reactions in methanol. Their reaction, however, was performed at a lower temperature than ours. Treatment of the fluorodi*iso*propylidenegalactose (II) with hydrated potassium fluoride in methanol at 150° for 17 hr. afforded only unchanged starting material. No evidence of methylation was found. It is suggested that at least two reactions are involved in the exchange reactions of primary sulphonic esters with potassium fluoride in methanol.

## Experimental

*Paper Chromatography.*—This was by downward elution on Whatman No. 1 paper with the water-poor phase of butan-1-ol–ethanol–water (4 : 1 : 5 v/v). Aldoses were detected by spraying the chromatogram with aniline hydrogen phthalate and heating it for 5—10 min. at 100°.[6]

*Detection of Fluorine.*—The substance (3—5 mg.) was fused with potassium, and the product

plunged into cold water (2 c.c.). After boiling with animal charcoal, the solution was filtered into a zirconium–alizarin solution [7] (0·1 c.c.). If fluorine was present the reddish-violet colour of the solution immediately changed to yellow.

The presence and analysis of fluorine in all fluoro-sugars and derivatives was confirmed by emission spectra.[8]

6-*Deoxy*-6-*fluoro*-1 : 2-3 : 4-*di*-O-iso*propylidene*-D-*galactopyranose* (II).—6-*O*-Methanesulphonyl-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactopyranose [9] (I), m. p. 120° (15 g.), anhydrous potassium fluoride (15 g.), and ethanediol (150 c.c.) were gently refluxed for 75 min. The solution was cooled, poured into water (750 c.c.), filtered, and extracted with ether (3 × 200 c.c.). The dried extract ($Na_2SO_4$) when evaporated gave a syrup (9 g.) which on distillation furnished 6-*deoxy*-6-*fluoro*-1 : 2-3 : 4-*di*-O-iso*propylidene*-D-*galactose* (5·6 g.), b. p. 70—72°/0·015 mm., $n_D^{20}$ 1·4475, $[\alpha]_D^{20}$ −51·4° (*c* 1·284 in $CHCl_3$) (cf. 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactopyranose, $n_D^{20}$ 1·4680, $[\alpha]_D^{20}$ −54·7° in $CHCl_3$ [10]) (Found: C, 55·1; H, 7·0; F, 7·0. $C_{12}H_{19}O_5F$ requires C, 55·0; H, 7·2; F, 7·2%).

*Methyl* 6-*Deoxy*-6-*fluoro*-α-D-*galactopyranoside* (IV).—6-Deoxy-6-fluoro-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactopyranose (2 g.) was refluxed in 1% methanolic hydrogen chloride (100 c.c.) for 5 hr. The solution was neutralised with lead carbonate, filtered, and evaporated to a non-reducing syrup. This was dissolved in a little acetone, the whole was filtered and ether was added. Gradually, at room temperature, crystals separated (0·35 g.). Methyl 6-deoxy-6-fluoro-α-D-galactopyranoside recrystallised from acetone–ether as needles, m. p. 139°, $[\alpha]_D^{20}$ +194° (*c* 0·103 in $H_2O$) (cf. methyl α-D-galactopyranoside,[11] $[\alpha]_D^{20}$ +196° in $H_2O$) (Found: C, 43·0; H, 6·7; OMe, 15·7; F, 9·5. $C_7H_{13}O_5F$ requires C, 42·8; H, 6·6; OMe, 15·8; F, 9·7%). Treatment of the *fluorogalactoside* with methanesulphonyl chloride in dry pyridine gave a crystalline *tri*-O-*methanesulphonate* which recrystallised from ethanol as needles, m. p. 185° (Found: C, 28·2; H, 4·4; F, positive. $C_{10}H_{19}O_{11}S_3F$ requires C, 28·0; H, 4·4%).

6-*Deoxy*-6-*fluoro*-α-D-*galactopyranose* (III).—6-Deoxy-6-fluoro-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactopyranose (2 g.) was heated in methanol (30 c.c.) and 0·02N-sulphuric acid (50 c.c.) at 100° for 4 hr. After neutralisation with 0·1N-barium hydroxide and filtration the solution was extracted with ether (2 × 100 c.c.). The aqueous layer was evaporated under reduced pressure to a syrup (0·75 g.) which was dissolved in absolute methanol–ether. 6-*Deoxy*-6-*fluoro*-α-D-*galactopyranose* gradually separated and recrystallised from ethanol–ether as needles, m. p. 160°, $[\alpha]_D^{20}$ +135° ⟶ +76·5° (*c* 0·967 in $H_2O$), $R_F$ 0·25 (cf. α-D-galactopyranose,[12] $[\alpha]_D^{20}$ +140° ⟶ +81·7°, $R_F$ 0·1) (Found: C, 39·12; H, 5·9; F, 10·0. $C_6H_{11}O_5F$ requires C, 39·5; H, 6·04; F, 10·4%).

The 2 : 5-*dichlorophenylhydrazone* was prepared by dissolving the free sugar (50 mg.) in absolute methanol (15 c.c.), adding 2 : 5-dichlorophenylhydrazine (50 mg.), and evaporating the solution to dryness on the boiling-water bath. Ether was added to the residue and the solid hydrazone crystallised from aqueous methanol as needles, m. p. 182° (Found: C, 42·3; H, 4·35; N, 8·1; F, positive. $C_{12}H_{15}O_4N_2Cl_2F$ requires C, 42·2; H, 4·4; N, 8·2; F, 5·6%).

*Methyl* 5-O-*Methanesulphonyl*-2 : 3-O-iso*propylidene*-β-D-*ribofuranoside* (VI).— Methyl 2 : 3-*O*-*iso*propylidene-αβ-D-ribofuranoside,[13] b. p. 83—85°/0·05 mm. (5·5 g.), was dissolved in dry pyridine (25 c.c.) containing methanesulphonyl chloride (5 c.c.) at −18°. The solution was set aside for 24 hr. at 2°, then poured into water (300 c.c.) and extracted with chloroform (3 × 150 c.c.). The extract was washed with 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water. After drying ($Na_2SO_4$), the solvent was removed *in vacuo* to leave a thick yellow syrup (8·6 g.) which crystallised spontaneously. The *product* recrystallised from methanol as needles (5 g.), m. p. 82°, $[\alpha]_D^{20}$ −56·7° (*c* 1·2 in MeOH) (Found: C, 42·5; H, 6·4; S, 11·1. $C_{10}H_{18}O_7S$ requires C, 42·1; H, 6·4; S, 11·4%). The ribofuranoside was assigned the β-configuration on the basis of its negative rotation.

*Methyl* 5-*Deoxy*-5-*fluoro*-2 : 3-O-iso*propylidene*-β-D-*ribofuranoside* (VII).—Methyl 5-*O*-methanesulphonyl-2 : 3-*O*-*iso*propylidene-β-D-ribofuranoside (4·5 g.) in ethanediol (45 c.c.) and

[6] Partridge, *Biochem. J.*, 1948, **42**, 238.
[7] Vogel, "Qualitative Inorganic Analysis," Longmans Green and Co., London, 1947, p. 272.
[8] Birks, *Spectrochim. Acta*, 1954, **6**, 169.
[9] Helferich, Dressler, and Griebel, *J. prakt. Chem.*, 1939, **153**, 285.
[10] Ohle and Berend, *Ber.*, 1925, **58**, 2585.
[11] Riiber, Minsaas, and Lyche, *J.*, 1929, 2173.
[12] Tanret, *Bull. Soc. chim. France*, 1896, **15**, 195.
[13] Levene and Stiller, *J. Biol. Chem.*, 1934, **104**, 299.

anhydrous potassium fluoride (4·5 g.) was refluxed gently ($CaCl_2$ tube) for 1 hr. The solution was cooled and poured into water (200 c.c.) and extracted with ether (2 × 200 c.c.). The extract was dried ($Na_2SO_4$) and evaporated (bath-temperature, 40°) to a mobile liquid, which on distillation gave the *fluororiboside* (VIII) (1·5 g.), b. p. 32°/0·025 mm., $n_D^{20}$ 1·4270, $[\alpha]_D^{20}$ −91·9° (*c* 1·097 in $CHCl_3$) (Found: C, 52·8; H, 7·4; OMe, 14·4; F, 9·0. $C_9H_{15}O_4F$ requires C, 52·5; H, 7·3; OMe, 15·05; F, 9·2%).

*5-Deoxy-5-fluoro-αβ-D-ribose* (VIII).—Methyl 5-deoxy-5-fluoro-2 : 3-*O*-*iso*propylidene-β-D-ribofuranoside (0·5 g.) was heated on a boiling-water bath with 0·02N-sulphuric acid (15 c.c.) for 3 hr. The solution was neutralised with 0·1N-barium hydroxide, and the filtrate extracted with ether (2 × 50 c.c.). The aqueous layer was evaporated to dryness *in vacuo*, giving 5-deoxy-5-fluoro-αβ-D-ribose as a colourless reducing syrup (0·3 g.), $R_F$ 0·4 (cf. D-ribose, 0·22). The 2 : 5-*dichlorophenylhydrazone*, made as above, crystallised on addition of light petroleum (b. p. 40—60°) to the ether solution as needles, m. p. 130° (Found: C, 42·5; H, 4·2; N, 8·8; F, 6·0. $C_{11}H_{13}O_3N_2Cl_2F$ requires C, 42·4; H, 4·2; N, 9·0; F, 6·1%).

3 : 5-O-*Benzylidene-6-deoxy-6-fluoro*-1 : 2-O-iso*propylidene*-D-*glucofuranose*.—3 : 5-*O*-Benzylidene-6-*O*-methanesulphonyl-1 : 2-*O*-*iso*propylidene-D-glucofuranose [1] (0·5 g.) was heated in ethanediol (5 c.c.) containing anhydrous potassium fluoride (0·5 g.) at the b. p. for 2·5 min. The dark solution was poured into water (75 c.c.) and extracted with ether (2 × 50 c.c.). Evaporation of the extract gave a syrup which, crystallised from methanol (yield 0·3 g.), had $[\alpha]_D^{20}$ +32·4° (c 1·9 in MeOH), m. p. 104—105° alone or in admixture with compound formed by methanolic exchange [1] (Found: C, 61·7; H, 5·6; F, positive. Calc. for $C_{16}H_{19}O_5F$: C, 61·9; H, 6·1%).

*Methyl 6-Deoxy-6-fluoro-α-D-glucopyranoside*.—6-Deoxy-6-fluoro-D-glucose [1] (0·5 g.) was heated with 1% (w/v) methanolic hydrogen chloride (40 c.c.) for 5 hr. Neutralisation with silver carbonate, filtration, and evaporation gave a syrup from which the *product* crystallised on addition of dry chloroform–light petroleum. It had m. p. 109—110°, $[\alpha]_D^{21}$ +43° (*c* 1·76 in $H_2O$) (Found: C, 42·7; H, 6·5; F, 10·0. $C_7H_{13}O_5F$ requires C, 42·8; H 6·7; F, 9·7%).

*Periodate Oxidations*.—0·1M-Sodium metaperiodate (10 c.c.) was added to solutions of methyl α-D-galactopyranoside (24·6 mg. in 10 c.c. of water), methyl 6-deoxy-6-fluoro-α-D-galactopyranoside (7·7 mg. in 10 c.c.), and methyl 6-deoxy-6-fluoro-α-D-glucopyranoside (25 mg. in 10 c.c.) all in glass-stoppered brown bottles. After intervals 2 c.c. portions were removed and immediately transferred into 3 c.c. of M-sodium hydrogen carbonate solution and 2 c.c. of 0·5M-potassium iodide. The iodine liberated was titrated with 0·05M-sodium thiosulphate. Results were as tabulated.

*Methyl α-D-galactopyranoside.*

| Time (min.) | 5 | 10 | 20 | 30 | (24 hr.) |
|---|---|---|---|---|---|
| $NaIO_4$ consumed (mols.) | 0·05 | 0·25 | 0·75 | 1·32 | 2·08 |

*Methyl 6-deoxy-6-fluoro-α-D-galactopyranoside.*

| Time (min.) | 5 | 10 | 20 | 30 | (24 hr.) |
|---|---|---|---|---|---|
| $NaIO_4$ consumed (mols.) | 1·6 | 1·8 | 1·9 | 1·99 | 1·99 |

*Methyl 6-deoxy-6-fluoro-α-D-glucopyranoside.*

| Time (min.) | 5 | 10 | 20 | 30 | (24 hr.) |
|---|---|---|---|---|---|
| $NaIO_4$ consumed (mols.) | 1·3 | 1·4 | 1·7 | 1·8 | 1·85 |

The authors thank Sir Rudolph Peters and Mr. D. R. Davies for their help and encouragement, Mr. F. T. Birks for performing spectrometric determinations of fluorine, and Mr. E. A. Vincent for technical collaboration.

DEPARTMENT OF BIOCHEMISTRY UNIVERSITY OF OXFORD. [*Received, May 13th*, 1957.]

XUM

## 169. *Entropy Changes in Isomerisations.*

By R. M. Gascoigne.

The assumption that relative stabilities of isomers can be assessed from enthalpy data alone is valid for several types of isomerisation for which thermodynamic data are available. It is not valid for the chain-branching rearrangements of the higher paraffins or for certain keto-enol isomerisations. The structural and other factors which determine the magnitude of entropy changes in isomerisations are examined.

Thermodynamic aspects of the cyclisation–rearrangement reactions of terpene biosynthesis are evaluated.

In current theoretical developments in organic chemistry, particularly conformational analysis,[1] much attention is paid to assessment of relative stabilities of isomers. Recently, Allinger [2] has pointed out that confusion may arise from inexact use of the word "stability" and Wheland [3] has discussed the different and sometimes contradictory meanings of the word. Strictly, "stability" can mean only thermodynamic stability: thus in comparing two isomers, A and B, the isomer B is more stable if it predominates at equilibrium, *i.e.*, if the free-energy change, $\Delta G$, is negative for the reaction A ⟶ B in specified conditions. The free-energy change, and hence the relative stability, is determined by the enthalpy (heat content) change and the entropy change in the relation $\Delta G = \Delta H - T\Delta S$.

The word "stability" is still frequently used in the old, discarded sense of "thermochemical stability" [3] or at least the tacit assumption is made that entropy changes are sufficiently small to permit relative stabilities of isomers to be estimated from thermochemical (enthalpy) data alone. Often this assumption is made because enthalpy differences can, in general, be estimated from structural considerations whereas free-energy differences usually cannot. Thus, enthalpy differences are often determined by fairly well-known structural factors such as non-bonded repulsions, angle strain, resonance, polar repulsions, etc. Conformational analysis, for example, consists largely of comparisons of stability based essentially on enthalpy data (which have, however, been supplemented by data from equilibration experiments with the assumption that the two types of data are comparable).

What is generally required is a knowledge of the sign, and if possible the approximate magnitude, of $\Delta G$ for an isomerisation (hypothetical or real), given the sign, and often the magnitude, of $\Delta H$. Thermodynamic data are now available for many organic compounds, particularly hydrocarbons,[4] and in Tables 1 and 2 are listed the values of $\Delta H$, $T\Delta S$, and $\Delta G$ for a variety of isomerisation reactions. Generally $T\Delta S$ is numerically less than $\Delta H$, so that $\Delta G$ and $\Delta H$ have the same sign; hence the assumption that relative stabilities can be qualitatively assessed from enthalpy data is, in many cases, justified.

In other cases, however, $T\Delta S$ is greater than $\Delta H$. Such cases are, as yet, hardly predictable because only a limited approach can be made towards assessment of entropy changes caused by structural changes.* The structure-dependent contributions to the entropy of a molecule are those due to rotation and vibration.[5] Hence arise the applicability of qualitative ideas of molecular symmetry, compactness and rigidity, and the large effects of certain structural changes, particularly chain branching, ring formation,

* For reactions in solution changes in solvation are also to be considered since these can cause large entropy (and enthalpy) changes. Some instructive examples are discussed by Chatt and Wilkins, *J.*, 1952, 273, 4300.

[1] Recent reviews: Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44; Dauben and Pitzer, "Steric Effects in Organic Chemistry" (ed. Newman), Wiley, New York, 1956, Ch. 1.

[2] Allinger, *J. Org. Chem.*, 1956, **21**, 915.

[3] Wheland, "Advanced Organic Chemistry," Wiley, New York, 2nd Edn., 1949, pp. 366 *et seq.*

[4] Rossini, Pitzer, *et al.*, "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," Carnegie Press, Pittsburg, 1953.

[5] Cf. Janz, *Quart. Rev.*, 1955, **9**, 229.

and ring expansion. (Alternatively, the effect of these structural changes could be attributed to the large decrease in degrees of freedom of the molecules undergoing reaction.) The magnitude of the entropy changes in these three reactions, as compared with other isomerisations, is shown by comparison of the $T\Delta S$ values in Tables 1 and 2.

From the data available, the chain-branching rearrangements of *n*-octane (Table 1, A; similar data are available [4] for several such rearrangements of this compound), and presumably also of higher paraffins, are the only set of examples where $T\Delta S$ is greater than $\Delta H$ for a *skeletal* isomerisation at ordinary temperature. Above certain temperatures,

TABLE 1. *Isomerisations involving large entropy changes.*

Values are in kcal./mole at 25° and atmospheric pressure; data were taken from ref. 4 unless otherwise indicated.

| | State | $\Delta H$ | $T\Delta S$ | $\Delta G$ |
|---|---|---|---|---|
| **A.** *Chain-branching rearrangements* | | | | |
| *n*-Butane ⟶ *iso*butane | gas | − 2·00 | − 1·10 | − 0·90 |
| *n*-Pentane ⟶ *neo*pentane | gas | − 4·67 | − 3·06 | − 1·61 |
| *n*-Hexane ⟶ 2 : 3-dimethylbutane | gas * | − 2·53 | − 1·61 | − 0·92 |
| *n*-Heptane ⟶ 2 : 2 : 3-trimethylbutane | gas * | − 4·07 | − 3·18 | − 0·89 |
| *n*-Heptane ⟶ 3-ethylpentane | gas * | − 0·45 | − 1·18 | + 0·73 |
| *n*-Octane ⟶ 4-methylheptane | gas * | − 0·87 | − 0·96 | + 0·09 |
| *n*-Octane ⟶ 3-ethyl-2-methylpentane | gas * | − 0·66 | − 1·82 | + 1·16 |
| *n*-Octane ⟶ 2 : 2 : 3 : 3-tetramethylbutane | gas * | − 4·17 | − 5·52 | + 1·35 |
| *n*-Butan-1-ol ⟶ 2-methylpropan-2-ol [a] | liq. | − 9·80 | − 2·76 | − 7·04 |
| *n*-Pentan-1-ol ⟶ 2-methylbutan-1-ol [a] | liq. | −10·40 | − 1·86 | − 8·54 |
| **B.** *Ring formation and fission* | | | | |
| *cyclo*Propane [b,c] ⟶ propene | gas | − 7·83 | + 2·09 | − 9·92 |
| *cyclo*Butane [b] ⟶ but-1-ene | gas | − 6·26 | + 2·88 | − 9·14 |
| Pent-1-ene ⟶ *cyclo*pentane | gas | −13·46 | − 3·77 | − 9·69 |
| Hex-1-ene ⟶ *cyclo*hexane | gas | −19·47 | − 6·16 | −13·31 |
| Hept-1-ene ⟶ *cyclo*heptane [d] | gas | −13·63 | − 5·79 | − 7·84 |
| Oct-1-ene ⟶ *cyclo*octane [d] | gas | −10·24 | − 6·82 | − 3·42 |
| Hept-1-ene ⟶ methyl*cyclo*hexane | gas | −22·10 | − 5·72 | −16·38 |
| Oct-1-ene ⟶ *trans*-1 : 2-dimethyl*cyclo*hexane | gas | −23·20 | − 6·54 | −16·66 |
| Oct-1-ene ⟶ ethyl*cyclo*hexane | gas | −21·23 | − 5·71 | −15·52 |
| Eicos-1-ene ⟶ *n*-tetradecyl*cyclo*hexane | gas | −21·28 | − 5·85 | −15·43 |
| Penta-1 : 4-diene ⟶ *cyclo*pentene | gas | −17·35 | − 3·13 | −14·20 |
| Hexa-1 : 5-diene [e] ⟶ *cyclo*hexene | gas | −21·96 | − 6·60 | −15·36 |
| *trans*-Deca-1 : 5-diene [e] ⟶ *trans*-decalin [f] | gas | −44 | −13·6 | −30 |
| **C.** *Ring expansion and contraction* | | | | |
| Methyl*cyclo*pentane ⟶ *cyclo*hexane | gas * | − 3·93 | − 2·99 | − 0·94 |
| 1-Methyl*cyclo*pentene ⟶ *cyclo*hexene | gas | — | − 1·11 | — |
| 1 : 1-Dimethyl*cyclo*pentane ⟶ methyl*cyclo*hexane | gas * | − 3·94 | − 1·14 | − 2·80 |
| *trans*-1 : 2-Dimethyl*cyclo*pentane ⟶ methyl*cyclo*hexane | gas * | − 4·32 | − 1·67 | − 2·65 |
| *trans*-1 : 3-Dimethyl*cyclo*pentane ⟶ methyl*cyclo*hexane | gas * | − 4·52 | − 1·67 | − 2·85 |
| Ethyl*cyclo*pentane ⟶ methyl*cyclo*hexane | gas * | − 6·62 | − 2·49 | − 4·13 |
| *cyclo*Heptane [d] ⟶ methyl*cyclo*hexane | gas * | − 8·47 | + 0·07 | − 8·54 |
| *cyclo*Octane [d] ⟶ ethyl*cyclo*hexane | gas * | −10·99 | + 1·13 | −12·12 |

* Data for the liquid state are available and are very similar.

[a] Parks and Huffman, "The Free Energies of Some Organic Compounds," Chemical Catalog Co., New York, 1932. [b] Rathjens, Freeman, Gwinn, and Pitzer, *J. Amer. Chem. Soc.*, 1953, **75**, 5634. [c] Ruehrwein and Powell, *ibid.*, 1946, **68**, 1063. [d] Finke, Scott, Gross, Messerly, and Waddington, *ibid.*, 1956, **78**, 5469. [e] $\Delta H_f$ and $S$ estimated by the method of Souders, Matthews, and Hurd, *Ind. Eng. Chem.*, 1949, **41**, 1048. [f] $\Delta H_f$ and $S$ for the gaseous state estimated as *ca.* −46 kcal./mole and 81 cal./degree/mole (see Appendix).

up to *ca.* 200°, $T\Delta S$ is greater than $\Delta H$ for the chain-branching rearrangements of most of the lower paraffins also. Isomerisations involving a change in *bond type* may be expected to exhibit appreciable entropy (and enthalpy) changes. This is the case, generally, in keto-enol equilibria of β-keto-esters, for which thermodynamic data are available (for the gaseous state).[6] Here $T\Delta S$ is often greater than $\Delta H$;[6] thus there is no

[6] Briegleb, Strohmeier, and Höhne, *Z. Elektrochem.*, 1952, **56**, 240; *Z. Naturforsch.*, 1953, **8***b*, 53; 1952, **7***b*, 184; 1951, **6***b*, 6.

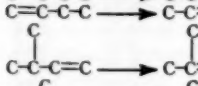
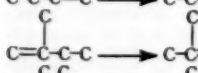
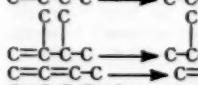
XUM

qualitative correlation between the enthalpy differences and the relative stability of the isomers; hence the numerous attempts to explain the equilibrium positions on purely thermochemical grounds are necessarily inadequate.

The small entropy changes in *cis–trans*-isomerisations (Table 2, A) are particularly striking. Thus, large variations in molecular shape can be accompanied by quite small

TABLE 2. *Isomerisations involving small entropy changes.*

Values are in kcal./mole at 25° and atmospheric pressure; data were taken from ref. 4 unless otherwise stated.

| | State | $\Delta H$ | $T\Delta S$ | $\Delta G$ |
|---|---|---|---|---|
| **A. cis ⟶ trans-*Isomerisation* (*additional to the examples listed by Chatt and Wilkins, J., 1952, 274*)** | | | | |
| Decalin [a] | liq. | − 2·12 | +0·28 | − 2·40 |
| 3-Methylpent-2-ene | gas | 0·00 | +0·24 | − 0·24 |
| 4-Methylpent-2-ene | gas | − 1·00 | −0·36 | − 0·64 |
| Propenylbenzene | gas | − 1·00 | −0·24 | − 0·76 |
| 1 : 2-Dichloroethylene [b] | gas | + 0·58 | +0·05 | + 0·53 |
| Maleic ⟶ fumaric acid [c] | solid | − 6·80 | +0·48 | − 7·28 |
| **B. *Mutarotation and epimerisation*** | | | | |
| β- ⟶ α-Glucose [d] | soln.[e] | 0 | +0·33 | − 0·33 |
| β- ⟶ α-Mannose [d] | soln.[e] | 0 | +0·25 | − 0·25 |
| α- ⟶ β-Xylose [d] | soln.[e] | − 0·55 | −0·18 | − 0·37 |
| α- ⟶ β-Lactose [d] | soln.[e] | + 0·71 | +1·01 | − 0·30 |
| β- ⟶ α-Glucose penta-acetate [f] | soln.[g] | − 1·39 | −0·42 | − 0·97 |
| Mannitol ⟶ Dulcitol [c] | solid | − 1·20 | −0·30 | − 0·90 |
| β-Maltose [h] ⟶ α-Lactose [h] | solid | − 5·9 | −0·2 | − 5·7 |
| **C. *Double-bond migration*** | | | | |
| C=C-C-C ⟶ C-C=C-C (*cis*) | gas | − 1·64 | −0·34 | − 1·30 |
| C=C-C-C ⟶ C-C=C-C(*trans*) | gas | − 2·64 | −0·65 | − 1·99 |
|  | gas | − 3·25 | +0·36 | − 3·61 |
|  | gas | − 1·49 | −0·35 | − 1·14 |
|  | gas | − 1·13 | −0·21 | − 0·92 |
| C=C=C-C ⟶ C=C-C=C | gas | −12·44 | −1·02 | −11·42 |
| C=C-C-C=C ⟶ C=C-C=C-C (*trans*) | gas | − 6·60 | −0·98 | − 5·62 |
| 3- ⟶ 1-Methyl*cyclo*pentene | gas | — | −0·30 | — |
| 1 : 5- ⟶ 1 : 2-Dimethyl*cyclo*pentene | gas | — | −0·72 | — |
| **D. 1 : 2-*Migration of methyl groups*** | | | | |
| 3- ⟶ 2-Methylpentane | gas[i] | − 0·64 | +0·05 | − 0·69 |
| 2 : 3- ⟶ 2 : 2-Dimethylbutane | gas[i] | − 1·86 | −0·53 | − 1·33 |
| 3-Ethyl-2-methyl- ⟶ 3-ethyl-3-methylpentane | gas[i] | − 0·90 | −0·58 | − 0·32 |
| *cis*-1 : 2- ⟶ 1 : 1-Dimethyl*cyclo*hexane | gas[i] | − 2·11 | −0·68 | − 1·43 |
| *trans*-1: 2- ⟶ *cis*-1 : 3-Dimethyl*cyclo*hexane | gas[i] | − 1·14 | −0·03 | − 1·11 |
| *trans*-1 : 4- ⟶ *cis*-1 : 3-Dimethyl*cyclo*hexane | gas[i] | − 0·04 | +0·41 | − 0·45 |
| *cis*-1 : 2- ⟶ 1: 1-Dimethyl*cyclo*pentane | gas[i] | − 2·09 | −0·49 | − 1·60 |
| *cis*-1 : 2- ⟶ *cis*-1 : 3-Dimethyl*cyclo*pentane | gas[i] | − 0·97 | +0·05 | − 1·02 |

[i] Data for the liquid state are available and are very similar.

[a] Parks and Hatton, *J. Amer. Chem. Soc.*, 1949, **71**, 2773. [b] Pitzer and Hollenberg, *ibid.*, 1954, **76**, 1493. [c] Ref. *a*, Table 1. [d] Kendrew and Moelwyn-Hughes, *Proc. Roy. Soc.*, 1940, **176**, *A*, 352. [e] In water. [f] Bonner, *J. Amer. Chem.*, 1951, **73**, 2659. [g] In acetic acid–acetic anhydride. [h] Monohydrate; Anderson and Stegeman, *J. Amer. Chem. Soc.*, 1941, **63**, 2119.

variations in molecular degrees of freedom. It is noteworthy that *trans*-isomers do not always have the lower entropy; *e.g.*, *trans*-decalin is more symmetrical and more rigid than *cis*-decalin and so might be expected to have the lower entropy but the opposite is the case. Clearly, qualitative considerations cannot predict the sign of small entropy changes. Recently, Allinger [2] has suggested that the discrepant stability relations in the

9-methyldecalin and hexahydroindane series may be due to entropy differences. However, from the nature of the data in Table 2, A, it is doubtful if this is the case.

Table 2, D, contains representative examples of methyl 1 : 2-migrations (for other examples, see ref. 4). The reactions listed, like those in Table 1, A and C, are formally equivalent to Wagner–Meerwein rearrangements. It may be concluded that in isomerisations (hypothetical or real) involving such rearrangements the relative stabilities of the isomers can safely be predicted from the relative enthalpies, with the exceptions, already noted, in the higher paraffins. Application of this principle is made in the following paper. Similar remarks apply to double-bond isomerisations, representative examples of which are listed in Table 2, C.

The conclusions reached in this paper are relevant to certain biosynthetical reactions which are of interest essentially as skeletal isomerisations. Ruzicka and his colleagues [7] have proposed a hypothesis in which the biosynthesis of the various classes of cyclic terpenes is thought to take place by cyclisation of aliphatic prototypes; thus the numerous cyclic triterpenes are derived by oxidative cyclisation of squalene. The complex cyclisations often incorporate several 1 : 2-shifts of methyl groups, hydrogen atoms, or ring members (ring expansion or contraction) and are envisaged to be single, "non-stop" reactions. By analogy with the reactions listed in Tables 1, B, 1, C, and 2, D, these reactions should be exothermic ($\Delta H$ negative) and $T\Delta S$ should be numerically less than $\Delta H$; hence they should also be exergonic ($\Delta G$ negative; thermodynamically spontaneous).

TABLE 3. *Estimated thermodynamic properties of representative triterpenes (hypothetical gaseous state; atmospheric pressure; 25°).*

$\Delta H_f$ and $\Delta S_f$ were calculated by the method of Souders, Matthews, and Hurd [13] and $\Delta H_f$ was corrected for various conformational features (see Appendix). Values of $\Delta S_f$ are in cal./degree/mole and other values are in kcal./mole.

| | $-\Delta H_f$ (calc.) | $-\Delta H_f$ (corr.) | $-\Delta S_f$ (calc.) | Formation from squalene: $-\Delta H$ | $-T\Delta S$ | $-\Delta G$ |
|---|---|---|---|---|---|---|
| Squalene | 12 | 12 | 534 | — | — | — |
| Ambrein | 144 | 137 | 654 | 125 | 36 | 89 |
| Tetra*cyclo*squalene | 92 | 90 | 628 | 78 | 28 | 50 |
| Onocerin | 172 | 169 | 661 | 157 | 38 | 119 |
| Lanosterol | 133 | 133 | 645 | 121 | 33 | 88 |
| Euphol | 133 | 127 | 645 | 115 | 33 | 82 |
| Dammaradienol | 130 | 126 | 651 | 114 | 35 | 79 |
| α-Amyrin | 155 | 147 | 681 | 135 | 44 | 91 |
| β-Amyrin | 155 | 146 | 682 | 134 | 44 | 90 |
| Taraxerol | 155 | 135 | 682 | 123 | 44 | 79 |
| Glutinol | 157 | 143 | 681 | 131 | 44 | 87 |
| Friedelin | 167 | 155 | 690 | 143 | 46 | 97 |
| Lupeol | 150 | 147 | 682 | 135 | 44 | 91 |
| Taraxasterol | 153 | 149 | 683 | 137 | 44 | 93 |

Clearly, the enzymic conversion of squalene into lanosterol [8] and the acid-catalysed conversion into tetra*cyclo*squalene [9] are exergonic reactions.

An estimate of the thermodynamic properties of terpenes can be made by methods used in petroleum technology. These methods have a sound theoretical basis [5] and depend upon the additivity of the enthalpy and entropy contributions of specific structural units; empirical correction factors are applied for various structural features. Thermodynamic properties of representative triterpenes estimated by one of these methods (discussed in the Appendix) are given in Table 3, together with the values of $\Delta H$, $T\Delta S$, and $\Delta G$ for their formation from squalene; these should be correct at least in order of

[7] Ruzicka, Eschenmoser, and Heusser, *Experientia*, 1953, **9**, 357; Eschenmoser, Ružicka, Jeger and Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890; Ruzicka, "Perspectives in Organic Chemistry" (ed. Todd), Interscience, New York, 1956 (cf. Stork and Burgstahler, *J. Amer. Chem. Soc.*, 1955, **77**, 5068).

[8] Tchen and Bloch, *J. Amer. Chem. Soc.*, 1955, **77**, 6085; 1956, **78**, 1516; cf. Clayton and Bloch, *J. Biol. Chem.*, 1956, **218**, 305, 319.

[9] Heilbron, Kamm, and Owens, *J.*, 1926, 1630.

magnitude. Necessarily, the estimates are for the gaseous state but the values for formation from squalene should not be significantly different for the liquid and the solid state.

As will be seen from Table 3, the reactions involved in the conversion of squalene into the various triterpenes are highly exergonic as well as exothermic. Stoicheiometrically, these reactions are not far removed from isomerisations and the $T\Delta S$ term has the same type of relation to $\Delta H$ as in the majority of examples in Tables 1 and 2; also the magnitudes of $\Delta H$, $T\Delta S$, and $\Delta G$ are what might be expected from extrapolation of values in Table 1, B.

Some support for the principle that each representative triterpene is formed directly from squalene by a single concerted reaction [7] is provided by consideration of relative thermodynamic stabilities. Taraxerol, glutinol, and friedelin could conceivably be formed by cyclisation of squalene to β-amyrin followed by rearrangement to these three compounds by reversal of the reactions discussed in the following paper. However, since taraxerol and glutinol are thermodynamically less stable than β-amyrin (see following paper) their formation from β-amyrin would involve a positive free-energy change of several kcal./mole. Endergonic reactions are, of course, common in the thermodynamically " open " systems of living organisms,[10,11] but it may well be doubted if they occur at the level of biosynthesis discussed here. In any case, coupling of the rearrangement of β-amyrin with a source of metabolic energy *via* energy carriers such as adenosine triphosphate [11,12] seems unlikely on mechanistic grounds.

Similar considerations apply in other terpene groups. Thus, in the monoterpenes it is well known that *in vitro* acyclic hydrocarbons are readily converted into monocyclic hydrocarbons but the latter are not converted into (strained) dicyclic hydrocarbons. Probably *in vivo* the dicyclic hydrocarbons are formed in a single reaction from the acyclic prototype and not from monocyclic hydrocarbons, since this would involve a positive free-energy change. Relevant $\Delta H$ values are: myrcene ⟶ limonene, −16·5; * myrcene ⟶ α-pinene, −7·4; limonene ⟶ α-pinene, +9·1. The free-energy changes in these reactions would have the same sign as the heat changes (cf. Table 1, B).

## Appendix

For the estimation of thermodynamic properties of triterpenes the method of Souders, Matthews, and Hurd [13] appeared the most suitable; group contributions for hydroxyl and keto-groups were taken from the similar method of Franklin.[14] Satisfactory estimates were obtained for monocyclic hydrocarbons, *e.g.*, 1 : 1-dimethyl*cyclo*hexane: $\Delta H_f$, −44·65 kcal./mole; $\Delta S_f$, −172·6 cal./degree/mole; the experimental values [4] are −43·26 and −173·6, respectively. The main source of error is probably in the application of the method to polycyclic systems; experimental data for such systems are meagre and so the method cannot distinguish between *cis*- and *trans*-ring junctions. The calculated values for decalin are: $\Delta H_f$, −42·3; $\Delta S_f$, −214·3; $\Delta G_f$, +21·9; experimental values for the gaseous state are available [15] only for $\Delta G_f$; these are: for the *cis*-isomer, +20·4, and for the *trans*-isomer, +17·6. Consequently, a rough correction of −4 kcal./mole per *trans*-junction was applied to the calculated values of $\Delta H_f$. This correction is similar to the adjacency corrections to $\Delta H_f$ made by Souders *et al.*[13]

Further approximate corrections, all positive in sign, were made to the calculated values of $\Delta H_f$ to allow for the main types of conformational instability. These were: for each diaxial 1 : 3-H : Me interaction, 0·9 kcal./mole; [16,17] for each diaxial 1 : 3-Me : Me interaction (and

* The $\Delta H$ values are in kcal./mole and are taken from Hawkins and Eriksen's combustion data (*J. Amer. Chem. Soc.*, 1954, **76**, 2669).

[10] Cf. Gutfreund, *Ann. Reports*, 1954, **51**, 295; *Adv. Enzymol.*, 1951, **11**, 1.
[11] Cf. Street, *Sci. Progr.*, 1950, **38**, 43.
[12] Cf. Avison and Hawkins, *Quart. Rev.*, 1951, **5**, 171.
[13] Souders, Matthews, and Hurd, *Ind. Eng. Chem.*, 1949, **41**, 1048.
[14] Franklin, *ibid.*, p. 1070.
[15] Parks and Hatton, *J. Amer. Chem. Soc.*, 1949, **71**, 2773; cf. Seyer, *ibid.*, 1953, **75**, 616.
[16] Beckett, Pitzer, and Spitzer, *ibid.*, 1947, **69**, 2488.
[17] Winstein and Holness, *ibid.*, 1955, **77**, 5562; Turner, *ibid.*, 1952, **74**, 2118.

two associated 1 : 3-H : Me interactions), 5·4 kcal./mole; [16] for each half-boat ring, 2·7 kcal./mole.[16]

I am indebted to Professor S. J. Angyal, Professor R. C. L. Bosworth, and Dr. R. L. Werner for valuable criticisms and suggestions.

N.S.W. University of Technology, Sydney. [*Received, May 13th*, 1957.]

[16] Beckett, Freeman, and Pitzer, *J. Amer. Chem. Soc.*, 1948, **70**, 4227.

---

## 170. *Triterpenes of the Friedelane Series. Part III.* The Course of the Friedelene–Oleanene Rearrangement.*

By J. L. Courtney, R. M. Gascoigne, and A. Z. Szumer.

The friedelene–oleanene rearrangement is not fully concerted since an intermediate, glutin-5(10)-ene (II), can be isolated. The latter is rearranged to olean-12-ene (VI) and in this conversion no intermediates could be detected. If taraxerene (IV) were an intermediate it would be too short-lived to be detectable by ordinary means. Thermodynamic considerations, based on conformational analysis, indicate that if intermediates are involved they would be transitory and could not be isolated.

The isolation of olean-12-ene establishes the configuration of $C_{(18)}$ in friedelane. Olean-12-ene is thought to be formed by proton elimination concerted with, and anti-parallel to, the migration of the $C_{(13)}$-methyl group.

An outstanding feature of triterpene chemistry is the number and variety of skeletal rearrangements involving 1 : 2-shifts of hydrogen atoms, methyl groups, or ring members. Such rearrangements are probably important in the biosyntheses of terpenes and steroids, and the conversion of squalene into cyclic triterpenes is thought to involve a variety of cyclisation-rearrangements (discussed in the preceding paper) which are fully concerted. Thus no intermediate is detectable in the enzymic conversion of squalene into lanosterol.[1]

The more spectacular rearrangements which have been observed *in vitro* include migration of several methyl groups and hydrogen atoms along the general plane of the triterpene molecule. The migrating groups are invariably in the axial configuration and so are perpendicularly above or below the general plane. Several such rearrangements have been observed in the oleanane and ursane series,[2] and the friedelene–oleanene rearrangement [3] is of this type. It proceeds by addition of a proton to the double bond of friedel-3-ene (I) forming a carbonium ion which undergoes a rearrangement incorporating 1 : 2-shifts of four methyl groups and two hydrogen atoms. Elimination of a proton followed by double-bond rearrangement yields finally an equilibrium mixture of olean-13(18)-ene (VIII) and 18α-olean-12-ene (IX).[4]

It would be of interest to know whether or not the movement of the several migrating groups, in such rearrangements, is fully or partially concerted. Thus in the friedelene–oleanene rearrangement the hydrocarbons (II), (III), and (IV) (and possibly also various double-bond isomers of these) might all exist as intermediates. We have followed this rearrangement polarimetrically in various conditions. In chloroform saturated with hydrogen chloride at room temperature (low proton-donating property) friedel-3-ene is converted into a double-bond isomer which will be discussed in a later

* Part II, *J.*, 1956, 2119.

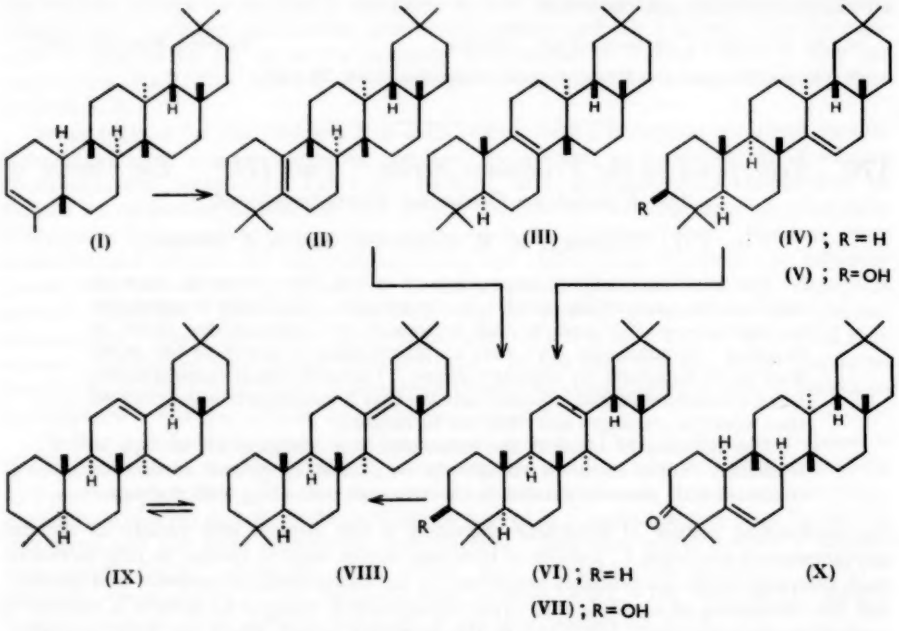
[1] Tchen and Bloch, *J. Amer. Chem. Soc.*, 1956, **78**, 1516.

[2] Spring *et al.*, *J.*, 1955, 3371, 3378; 1956, 465.

[3] (*a*) Brownlie, Spring, Stevenson, and Strachan, *Chem. and Ind.*, 1955, 686, 1156; *J.*, 1956, 2419; (*b*) Corey and Ursprung, *J. Amer. Chem. Soc.*, 1955, **77**, 3667, 3668; 1956, **78**, 5041; (*c*) Dutler, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1955, **38**, 1268.

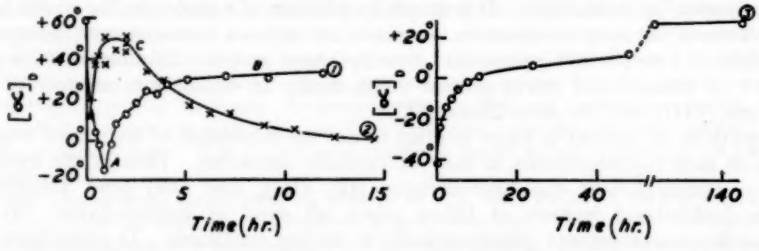
[4] Brownlie, Fayez, Spring, Stevenson, and Strachan, *J.*, 1956, 1377.

paper. However, when hydrogen chloride is passed through a solution of friedel-3-ene in boiling acetic acid more extensive changes occur. Fractional crystallisation of the mixture obtained after 1 hr. (point *A*, curve 1) yielded glutin-5(10)-ene (II), $[\alpha]_D$




−42°, as the major component.[5] Since this compound was converted by vigorous treatment by acid into the equilibrium mixture of olean-13(18)-ene and 18α-olean-12-ene it must be an intermediate in the friedelene–oleanene rearrangement and its

*Polarimetric rate curves for the rearrangement of* (1) *friedel-3-ene in boiling glacial acetic acid saturated with hydrogen chloride*; (2) *friedel-3-ene in a boiling* 1 : 20 *mixture of* 10N-*hydrochloric acid and glacial acetic acid*; (3) *glutin-5(10)-ene in chloroform saturated with hydrogen chloride at ordinary temperature.*




isolation proves that the rearrangement is not fully concerted, at least in the conditions used. The same skeletal change (I ⟶ II) occurs in the dehydrobromination of 4-bromofriedelin with silver acetate, which yields a mixture of glutin-5-en-3-one (X) and glutin-5(10)-en-3-one.[3b, 6]

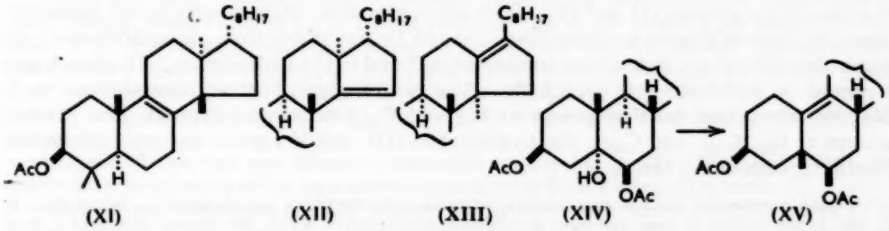
When glutin-5(10)-ene was treated with hydrogen chloride in boiling glacial acetic acid for several hours the specific rotation rose steadily to a nearly constant value and the

[5] Courtney, Gascoigne, and Szumer, *Chem. and Ind.*, 1956, 1479.
[6] Spring, Beaton, Stevenson, and Stewart, *Chem. and Ind.*, 1956, 1054.

hydrocarbon mixture obtained was identical (infrared spectra) with that from similar treatment of friedel-3-ene (point *B*, curve 1). An extensive fractional crystallisation of this mixture yielded glutin-5(10)-ene and olean-12-ene (VI), $[\alpha]_D$ +96°. That other compounds were present was indicated by comparison of the infrared spectrum of the mixture with that of a 1 : 1 mixture of glutin-5(10)-ene and olean-12-ene. Comparison of these spectra with the spectrum of the mixed crystal of olean-13(18)-ene and 18α-olean-12-ene suggested that one, or both, of these was present; they are known to be formed by isomerisation of olean-12-ene.[4] However, olean-12-ene is unaffected by hydrogen chloride in chloroform (room temp.) and when glutin-5(10)-ene was treated with this reagent it yielded, after 145 hr. (curve 3), a product whose infrared spectrum was very similar to that of the synthetic mixture of olean-12-ene and glutin-5(10)-ene; the spectrum gave no indication of any other component.

It is thus apparent that glutin-5(10)-ene (II) is converted into olean-12-ene (VI) and that no intermediates are detectable by the methods used. (The polarimetric curves contain some slight but reproducible irregularities; these may be due to transient formation of small amounts of double-bond isomers such as glutin-5-ene.) Of the two conceivable intermediates (III and IV) the former is unknown but the latter, taraxerene, occurs in Nature [7] and its constitution is known from that of its naturally-occurring 3β-hydroxy-derivative, taraxerol (V).[8] Beaton, Spring, Stevenson, and Stewart [8] observed that brief acid treatment of taraxeryl acetate yields β-amyrin acetate (as VII) and we have investigated the rate of conversion of taraxerene (IV) into olean-12-ene (VI). In the mildest conditions (chloroformic hydrogen chloride at room temp.) the rate was too fast to be measured, conversion into olean-12-ene being complete in less than 3 min. Hence, if taraxerene were an intermediate in the rearrangement of glutin-5(10)-ene to olean-12-ene it would not be detectable by ordinary methods. For conformational reasons, discussed below, the unknown hydrocarbon (III) would probably behave similarly.

The acid-catalysed conversion of olean-12-ene into the equilibrium mixture of olean-13(18)-ene (VIII) and 18α-olean-12-ene (IX) [4] may be regarded as the third and final stage of the friedelene–oleanene rearrangement. Friedel-3-ene was converted into this mixture in less than an hour by a boiling mixture of 10N-hydrochloric acid and acetic acid (1 : 5 v/v). In less acidic conditions (1 : 20 mixture) the conversion took about 14 hr. (curve 2) and olean-12-ene appeared to be formed (point *C*, curve 2) but could not be isolated pure; however, oxidation of the mixture with selenium dioxide in acetic acid and chromatography of the product gave olean-11 : 13(18)-diene in good yield. (Reproducibility was poor in this part of curve 2 presumably because of an interplay of double-bond rearrangements.)



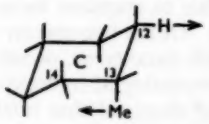

(XI) (XII) (XIII) (XIV) (XV)

The conversion of friedel-3-ene into olean-12-ene clarifies the only doubt concerning the stereochemistry of friedelane: the configuration of $C_{(18)}$ must be the same as in oleanane and the D/E ring junction must be *cis* as previously suggested.[3] Since glutin-5(10)-ene is an intermediate in the friedelene–oleanene rearrangement, no conclusions can

[7] Bruun, *Acta Chem. Scand.*, 1954, **8**, 1291.
[8] Beaton, Spring, Stevenson, and Stewart, *J.*, 1955, 2131.

be drawn from the rearrangement concerning the configurations of $C_{(5)}$ and $C_{(10)}$ in friedelane. The absolute configurations of these centres have, however, been established from other considerations.[3b, 9] The configuration of $C_{(8)}$ has been similarly established, and whether the rearrangement of glutin-5(10)-ene to olean-12-ene is concerted or not the configurations of $C_{(9)}$, $C_{(13)}$, and $C_{(14)}$ (as well as of $C_{(17)}$ and $C_{(18)}$) can be deduced from it.

Formation of olean-12-ene (VI) from glutin-5(10)-ene (II) or from taraxerene (IV) must involve elimination of a proton from $C_{(12)}$ instead of from $C_{(18)}$, even though the latter would yield the thermodynamically more stable isomer, olean-13(18)-ene (VIII). This indicates that the proton elimination is concerted with migration of the methyl group from $C_{(13)}$ to $C_{(14)}$ (see inset). The concerted process would be facilitated (and may only occur) by elimination of the proton in a direction antiparallel to the movement of the methyl group; the process would thus resemble a bimolecular elimination reaction. This geometrical requirement is satisfied by the equatorial ($\alpha$) hydrogen atom at $C_{(12)}$ but not by the hydrogen atom at $C_{(18)}$ which is axial in friedelane and related structures. In the similar rearrangement of euphenyl acetate (XI) to *iso*euphenyl acetate (XIII)[10] the $C_{(17)}$-hydrogen atom may satisfy the geometrical requirement, or alternatively, a $\Delta^{12}$-isomer, as initial product, may be isomerised to (XIII). In the rearrangement leading to Westphalen's diol (XIV ⟶ XV)[11] the direction of proton elimination appears to be the opposite of the present case; here again a $\Delta^{1(10)}$-isomer may be an intermediate or the proton elimination may not be concerted with the rearrangement.




The driving force for the friedelene–oleanene rearrangement has been attributed to the *cis*-locking of rings D and E in friedelene.[3a] This must cause marked steric instability, particularly because it results in close approach of the $\alpha$-oriented axial methyl groups attached to $C_{(13)}$ and $C_{(20)}$; inspection of models shows that, in consequence, ring E must be distorted and apparently cannot be in either a pure chair or a pure boat conformation. This feature is present also in glutin-5(10)-ene, the hydrocarbon (III), and taraxerene, and is undoubtedly the main cause of the rearrangement leading to olean-12-ene since it is absent from this compound. It cannot, however, be the cause of the rearrangement of friedel-3-ene to glutin-5(10)-ene; here the conformational driving force is provided by compression energy due to the proximity (1 : 3-interaction)[12] of the axial methyl groups at $C_{(5)}$ and $C_{(9)}$ in friedel-3-ene. The magnitude of such compression energy is indicated by the estimate[13] that the diaxial conformation of *cis*-1 : 3-dimethyl*cyclo*hexane is *ca.* 5·4 kcal./mole less stable than the diequatorial conformation (1 : 3-H : Me interactions are involved as well as the Me : Me interaction).

Glutin-5(10)-ene is thus conformationally more stable than friedel-3-ene; however, the two hydrocarbons (III and IV), which are conceivable intermediates in the rearrangement of glutin-5(10)-ene to olean-12-ene, would be *less* stable than glutin-5(10)-ene. In taraxerene (IV) ring C is in a boat conformation * and in the hydrocarbon (III) rings B and C would be half-boats (cf. euphol[10a]). Also, whilst glutin-5(10)-ene contains one 1 : 3-Me : Me interaction (methyl groups at $C_{(9)}$ and $C_{(14)}$) taraxerene contains two (methyl groups at $C_{(4)}$, $C_{(10)}$, and $C_{(8)}$); the hydrocarbon (III) would contain one such interaction (methyl groups at $C_{(4)}$ and $C_{(10)}$).

* Conformationally the C/D ring junction of taraxerene resembles a *trans*-junction, hence rings B, C, and D are similar to *trans-syn-trans*-perhydrophenanthrene in which the central ring is in a boat conformation (Johnson, *Experientia*, 1951, **8**, 315; *J. Amer. Chem. Soc.*, 1953, **75**, 1498).

[9] Takahashi and Ourisson, *Bull. Soc. chim. France*, 1956, **353**; Courtney, Gascoigne, and Szumer, *J.*, 1956, 2119; Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362.

[10] (*a*) Barton, McGhie, Pradhan, and Knight, *Chem. and Ind.*, 1954, 1325; *J.*, 1955, 876; (*b*) Arigoni, Viterbo, Dünnenberger, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1954, **37**, 2306.

[11] Petrov *et al.*, *J.*, 1938, 677; 1939, 998; 1952, 2246; Bladon, Henbest, and Wood, *J.*, 1952, 2737.

[12] Cf. Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44; Dauben and Pitzer, "Steric Effects in Organic Chemistry" (ed. Newman), Wiley, New York, 1956, Chap. 1.

[13] Beckett, Pitzer, and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488.

Since the hydrocarbons (III and IV) are conformationally less stable than glutin-5(10)-ene, and since they differ from it only in carbon skeleton, they are thermodynamically less stable (cf. preceding paper). Hence if they were intermediates in the rearrangement they would not be isolable (cf. the impossibility of isolating *cyclo*hexadiene in the hydrogenation of benzene [14]). The present work yields no evidence as to whether or not the glutin-5(10)-ene ⟶ olean-12-ene rearrangement is concerted, but indicates that positive evidence, either way, would be difficult to obtain.

The rearrangement of euphenyl acetate (XI) to *iso*euphenyl acetate (XIII) [10] is similar. Here the compound (XII) is conceivably an intermediate. It is probably identical with *apo*euphenyl acetate, prepared indirectly from butyrospermol; [15] if so, it would not be an isolable intermediate since *apo*euphenyl acetate is rearranged to *iso*euphenyl acetate by acid much more rapidly than is euphenyl acetate.[15]

The stability sequence, olean-12-ene > glutin-5(10)-ene > taraxerene, would be paralleled in β-amyrin, glutinol, and taraxerol. However, although friedel-3-ene is less stable than olean-12-ene, probably by several kcal./mole because of the steric congestion in the ring E area, nevertheless friedelin is more stable (thermochemically and probably thermodynamically) than β-amyrin. Olean-12-ene and friedel-3-ene contain the same type (and number) of bonds but β-amyrin and friedelin differ in that the former contains the bonds C–O, O–H, and C=C in place of C=O, C–H, and C–C in the latter. In terms of bond energies [16] this feature stabilises friedelin by 15 kcal./mole, which would be greater than the energy difference due to the steric factor.

## Experimental

Analyses are by Dr. E. Challen and Mr. D. Weeden, and infrared spectra by Mr. I. Reece.

Specific rotations were measured in chloroform and, unless otherwise stated, in a 1 dm. tube. Chloroform used for the isomerisation experiments contained 2·0% of alcohol and the acetic acid had f. p. 14·8°. In the polarimetric runs with acetic acid as solvent each point was determined by isolating the solute (by dilution with water and extraction with chloroform) and measuring its specific rotation in chloroform solution.

*Friedel-3-ene.*—A solution of friedelin (20 g.) in hot benzene (400 ml.) was added to a suspension of lithium aluminium hydride (20 g.) in ether (1 l.) and the mixture was refluxed for 8 hr. Excess of lithium aluminium hydride was destroyed with ethyl acetate, and the crude *epi*friedelanol (19 g.) dissolved in pyridine (1·5 l.); phosphorus oxychloride (150 ml.) was then added slowly. The solution was left overnight, then boiled for 5 min., cooled, and poured into ice-water. The product was dissolved in benzene, and the solution filtered through alumina (500 g.), yielding friedel-3-ene (14 g.) as prisms (from alcohol–benzene), m. p. 253—256°, $[\alpha]_D$ +59° (*c* 0·5; 2 dm. tube). Lit.: [3d] m. p. 250—258°, 261—264° (vac.), $[\alpha]_D$ +53°.

*Glutin-5(10)-ene.*—When a stream of hydrogen chloride was passed through a suspension of finely ground friedel-3-ene (3 g.) in boiling acetic acid (2 l.) the friedel-3-ene soon dissolved. After 1 hr. the solution was concentrated to *ca.* 250 ml. and the product was repeatedly recrystallised from alcohol–benzene, yielding glutin-5(10)-ene as laths, m. p. 226—227°, $[\alpha]_D$ −42° (*c* 0·9)(Found: C, 87·7; H, 12·1. Calc. for $C_{30}H_{50}$: C, 87·7; H, 12·3%). Chapon [17] records m. p. 226°, $[\alpha]_D$ −38°, for a hydrocarbon which must have been glutin-5(10)-ene (cf. ref. 5).

Glutin-5(10)-ene was also obtained, somewhat impure (m. p. 222—225°, $[\alpha]_D$ −32°), by fractional crystallisation of the least soluble fraction from the following experiment.

*Olean-12-ene.*—Hydrogen chloride was passed through a solution of friedel-3-ene (3 g.) in boiling acetic acid (2 l.) for 7 hr. The solution was then concentrated (first to *ca.* 500 ml.) so as to give three crops of crystals. The third crop, which was initially gummy, after one recrystallisation from acetic acid had $[\alpha]_D$ +70° and on repeated recrystallisation yielded olean-12-ene, m. p. 160—161°, $[\alpha]_D$ +96° (*c*, 1·0), identical (infrared spectra) with an authentic

[14] Janz, *J. Chem. Phys.*, 1954, **22**, 751.
[15] Lawrie, Hamilton, Spring, and Watson, *J.*, 1956, 3272.
[16] Wheland, "Resonance in Organic Chemistry," Wiley, New York, 1955, p. 88, cf. p. 115 *et seq.*
[17] Chapon, *Bull. Soc. chim. France*, 1955, 1076, 1630.

specimen. It was characterised by oxidation with selenium dioxide in acetic acid to olean-11 : 13(18)-diene, m. p. 215—217°, $[\alpha]_D$ −66° (*c*, 0·7), $\lambda_{max.}$ 2420, 2510, 2600 Å ($\varepsilon$ 26,400, 30,600, and 19,800), identical (infrared spectra) with an authentic specimen.

Olean-12-ene was also obtained, slightly impure (m. p. 157—159°, $[\alpha]_D$ +91°), by fractional crystallisation of the material from the acetic acid mother-liquors from the above-described preparation of glutin-5(10)-ene.

*Taraxer-14-ene.*—Taraxerol (isolated from *Litsea dealbata* [18]) was oxidised with chromic acid according to Koller *et al.*,[19] yielding taraxerone, m. p. 241—244°, $[\alpha]_D$ +10° (*c* 2·0). Wolff–Kishner reduction of taraxerone (190 mg.) with anhydrous hydrazine at 200° for 16 hr. and filtration of a solution of the product in hexane through alumina yielded taraxer-14-ene (130 mg.) which crystallised from methanol–chloroform in laths, m. p. 242—244°, $[\alpha]_D$ +3° (*c* 1·0). Lit.: [20] m. p. 238—243°, $[\alpha]_D$ +3°, and m. p. 240—241°, $[\alpha]_D$ + 3°.

When hydrogen chloride was passed through a solution of taraxer-14-ene (48 mg.) in chloroform (10 ml.) the specific rotation rose to +98° in less than 3 min. and remained constant thereat. The product obtained by evaporation of the solvent had infrared absorption identical with that of olean-12-ene and after one recrystallisation from chloroform–methanol had m. p. 161—162°.

We are indebted to Mr. W. J. Dunstan for a gift of taraxerol.

ORGANIC CHEMISTRY DEPARTMENT,
N.S.W. UNIVERSITY OF TECHNOLOGY, SYDNEY. [*Received, May 13th*, 1957.]

[18] Dunstan, Hughes, and Smithson, *Austral. J. Chem.*, 1953, **6**, 321.
[19] Koller, Hiestand, Dietrich, and Jeger, *Helv. Chim. Acta*, 1950, **33**, 1050.
[20] Brooks, *J.*, 1955, 1675; Elsevier's "Encyclopædia of Organic Chemistry," Vol. 14, p. 1195S.

---

## 171. *A Nuclear Magnetic Resonance Study of the Hydrates of Molybdenum Trioxide.*

By S. MARIČIĆ and J. A. S. SMITH.

A combined proton magnetic resonance and infrared study has been made of the mono- and the di-hydrate of molybdenum trioxide. The results support the structures $MoO_3.H_2O$ and $MoO_3.2H_2O$, the separation of the hydrogen nuclei in the water molecules being 1·56 ± 0·03 Å in both compounds.

MOLYBDENUM TRIOXIDE DIHYDRATE, $MoO_3.2H_2O$, forms as yellow crystals when a solution of ammonium molybdate in fairly concentrated nitric acid is stored for a long time. Its obvious formulation is either as the hydrate of molybdic acid, $MoO_2(OH)_2.H_2O$, or as a simple hydrate of $MoO_3$. However, a preliminary *X*-ray investigation of the crystal showed that the structure was similar to that of $BaUO_4$, suggesting the formulation $(H_4O)^{2+}MoO_4^{2-}$, although subsequent refinement of the data has not confirmed this structure.[1] The presence in the solid state of any large concentrations of $H_4O^{2+}$ ions is extremely unlikely, and very strong confirmation of their presence would be required. The existence of a definite monohydrate has been established by both *X*-ray [2,3] and tensioeudiometric methods;[4] neither definitely establishes whether the structure is $H_2MoO_4$ or $MoO_3.H_2O$.

This paper discusses proton magnetic resonance experiments carried out on the monohydrate and dihydrate in an attempt to resolve these problems.[5] The general features of

[1] Lindqvist, *Acta Chem. Scand.*, 1956, **10**, 1361; see also *idem, ibid.*, 1950, **4**, 650.
[2] Buerger, *Z. anorg. Chem.*, 1922, **121**, 224.
[3] Funaki and Segawa, *J. Electrochem. Soc. Japan*, 1950, **18**, 307.
[4] Hüttig, *Z. angew. Chem.*, 1922, **35**, 391; Hüttig and Kurre, *Z. anorg. Chem.*, 1923, **126**, 167.
[5] Maričić and Smith, *Acta Chem. Scand.*, 1956, **10**, 1362.

such investigations in the solid state have often been discussed;[6,7] the criterion we shall use here is that water molecules, if they exist in the crystal, should possess a characteristic proton resonance spectrum, very similar to those found in previous measurements on other hydrates[8] but different from that expected from an $H_4O^{2+}$ ion, which should resemble the spectrum of the ammonium ion in ammonium chloride.

## Experimental

The sample of $MoO_3,2H_2O$, kindly supplied by Dr. I. Lindqvist, had been prepared by crystallisation for some years from an acid solution of ammonium molybdate and had been about one year in air. Chemical analysis revealed the presence of 0·057% w/w of ammonium ion, which would not be expected to produce a detectable nuclear resonance signal under the experimental conditions.

Proton resonance measurements were made at 16·435 Mc./sec. in a radiofrequency bridge type of apparatus, details of which have been given previously.[9] Radiofrequency levels in the bridge were kept below saturation in recording the spectra and the 25 c./sec. modulation never exceeded an amplitude of 1·2 gauss, so that the corresponding corrections to the second moment[10] were less than 1½%. These corrections have been applied to all second-moment values quoted here. The lines were usually recorded with a sweep rate of about 3 gauss per min., and the final time constant on the recorder channel was 9 sec. The inhomogeneity and the fluctuations in the magnetic field were both of the order of 1 part in $10^4$. Line shapes were recorded for samples ranging in composition from $MoO_3,2H_2O$ to $MoO_3,1{\cdot}1H_2O$, and at temperatures of 77° K and 290° K.

The infrared spectra of $MoO_3,2H_2O$, $MoO_3,1{\cdot}1H_2O$, and $MoO_3$ were recorded on a Grubb-Parsons S4 double-beam spectrometer. The samples were compressed in previously-ignited potassium chloride and the usual precautions were taken to exclude water.

The sample of $MoO_3$ was prepared from the dihydrate by ignition in air at 560° c and was pale ivory. The sample of composition $MoO_3,1{\cdot}1H_2O$ was prepared by slow dehydration of the dihydrate at room temperature in a vacuum desiccator at a pressure of about 2 mm. The process took over three weeks and the water lost corresponded to a residue of mean composition $MoO_3,1{\cdot}12H_2O$. Complete dehydration to the monohydrate would have taken at least another month unless the sample were heated. We assume here that the infrared and nuclear resonance spectra of this mixture of hydrates will be largely characteristic of the monohydrate.

## Results and Discussion

At 77° K the second moments of the absorption curves were $30{\cdot}7 \pm 1{\cdot}6$ gauss$^2$ for $MoO_3,2H_2O$ and $27{\cdot}6 \pm 1{\cdot}4$ gauss$^2$ for $MoO_3,1{\cdot}1H_2O$. These values, with their standard deviations, are the mean of at least five measurements. Typical derivative curves for the two hydrated samples are given in Figs. 1 and 2; the small double-headed arrow in each Figure indicates the peak-to-peak amplitude of the modulation. The curve for $MoO_3,1{\cdot}1H_2O$ is in many respects typical of that obtained from powdered gypsum,[11] with the exception of the small additional peaks at the centre of the curve. In order to provide additional confirmation of the hydrate structure, the theoretical curve for a water molecule was calculated by assuming a " rigid lattice " and an inter-proton distance of 1·58 Å (so that the value of the parameter $\alpha = \frac{3}{2}\mu r^{-3}$ is $5{\cdot}36_3$ gauss). Values of 1·58 Å have been found in $CaSO_4,2H_2O$,[11] 1·57 Å in $Li_2SO_4,H_2O$,[12] and 1·56 Å in $Ba(ClO_3)_2,H_2O$.[13] We used Pake's method of calculation[11] and computed two curves for values of the intermolecular broadening function, $\beta^2$, of 4·60 and 5·60 gauss$^2$. The comparison of the theoretical absorption curves with two sets of experimental data, given in Fig. 3, shows that better

[6] Andrew, " Nuclear Magnetic Resonance," Cambridge University Press, 1955, chap. 6.
[7] Smith, *Quart. Rev.*, 1953, **7**, 279.
[8] Wertz, *Chem. Rev.*, 1956, **55**, 829.
[9] Smith, *Discuss. Faraday Soc.*, 1955, **19**, 207.
[10] Andrew, *Phys. Rev.*, 1953, **91**, 425.
[11] Pake, *J. Chem. Phys.*, 1948, **16**, 327.
[12] Soutif, Dreyfus, and Ayant, *Compt. rend.*, 1951, **233**, 395.
[13] Spence, *J. Chem. Phys.*, 1955, **23**, 1166.

agreement is obtained with the curve for which $\beta^2 = 5{\cdot}60$ gauss$^2$ except at the centre of the line, where a small additional peak appears. One possible impurity which might give rise to this narrow line is a small concentration of hydroxyl groups; less than 1% of the total hydrogen, an amount difficult to detect analytically, would be sufficient to give rise to the effect. Groups like $NH_4^+$ or $H_3O^+$ would not give rise to such a narrow line unless they were allowed considerable freedom of movement at 77° K. Whatever the origin of the central peak its effect on the second moment will be very small.

Rather similar experimental curves were obtained from $MoO_3,2H_2O$, but the signal-to-noise ratio was poorer. The best agreement with theory in this case was obtained with a curve calculated for a water molecule of the same inter-proton distance (1·58 Å) as in the

FIG. 1. *Derivative curve of* $MoO_3,2H_2O$ *at* 77° K.

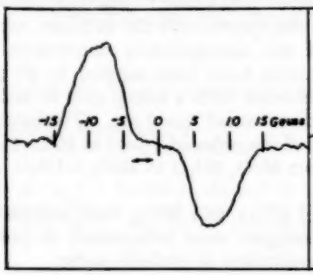



FIG. 2. *Derivative curve of* $MoO_3,1{\cdot}1H_2O$ *at* 77° K.

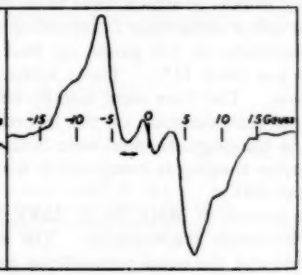
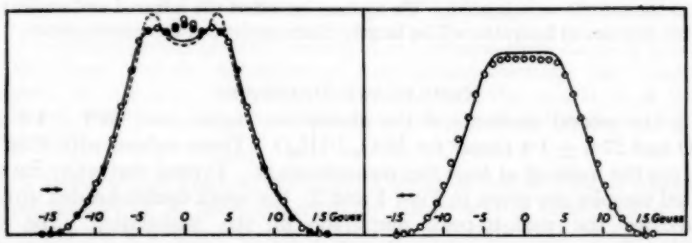



FIG. 3. *Comparison of the theoretical and experimental absorption curves for* $MoO_3,1{\cdot}1H_2O$ (*full line*, $\beta^2 = 5{\cdot}6$; *broken line*, $\beta^2 = 4{\cdot}6$ *gauss*$^2$).

FIG. 4. *Comparison of the theoretical and experimental absorption curves for* $MoO_3,2H_2O$ ($\beta^2 = 7{\cdot}7$ *gauss*$^2$).




monohydrate but with a value for $\beta^2$ of 7·70 gauss$^2$. A comparison of the two is given in Fig. 4. Again there is a poor fit at the centre of the curve, presumably arising from the same impurities that have been discussed in the case of the monohydrate. In this compound and possibly the monohydrate the high values of $\beta^2$ suggest that the water molecules approach quite closely.

For example, if we take into account only nearest-neighbour interactions, an intermolecular broadening of 7·70 gauss$^2$ would be provided by two protons at 2·13 Å to each proton of the water molecule or from four protons at 2·39 Å, compared with the value of about 2·30 Å expected in ice. The most probable arrangement cannot be predicted without more accurate information on the location of the oxygen atoms in the crystal. This would also tell us to what extent the assumption of a two-spin system for the water molecules is correct.

The value of 1·58 Å as obtained above is subject to serious systematic errors due to the thermal oscillations of the protons. Corrections to allow for this have been given by

Deeley and Richards,[14] Gutowsky, Pake, and Bersohn,[15] and Ibers and Stevenson.[16] We shall use here the method due to the last-named, and the infrared data mentioned later. In calculating the correction due to the vibrations of the water molecule, for which only the antisymmetric stretching frequency ($S_3$ in ref. 17) need be considered, we took $\nu_3$ as 3150 cm.$^{-1}$, $r$ as 1·58 Å and ∠HOH as 104° 28′. Unfortunately, the magnitudes of the two torsional frequencies which change θ are not known, but for the purpose of this calculation we used the mean of the two lowest infrared frequencies observed, 909 and 926 cm.$^{-1}$, which are absent from the spectrum of $MoO_3$, so that our calculation still contains an uncertainty. The corrected value of $\langle r^3 \rangle^{\frac{1}{3}}$ is then 1·56 Å. The standard deviation of the random errors is ±0·015 Å; allowing a reasonable value for the uncertainty mentioned above, we estimate the total s.d. to be ±0·03 Å.

What agreement there exists between the theoretical and experimental results is not

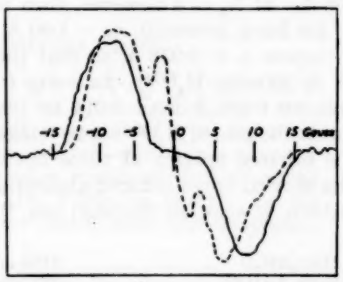



FIG. 5. *Comparison of the derivative curves of* $MoO_3,2H_2O$ *(full curve) and* $(CO_2H)_2,2H_2O$ *(broken curve) recorded at* 77° K.

improved by assuming the structure $MoO_2(OH)_2,H_2O$. An analogous configuration occurs in oxalic acid dihydrate, $(CO_2H)_2,2H_2O$,[18,19] and the derivative curve of this compound shows significant differences from that of the present hydrate. A comparison of the two curves recorded under similar conditions at 77° K is made in Fig. 5. Measurements on the present equipment suggest that the second-moment values for oxalic acid dihydrate are higher than previously reported.[18] The mean of four measurements at 77° K is 23·4 ± 1·4 gauss$^2$ and $(\Delta H)_{m.s.}$ is 13·4 gauss. The outer peaks of the curve, due largely to the water molecule, are similar in shape although different in separation, but the two curves behave quite differently near the centre where the contributions from the hydroxyl groups should predominate and be twice as great for the structure $MoO_2(OH)_2,H_2O$ as for $(CO_2H)_2,2H_2O$, so that the evidence from the line shape alone is fairly conclusive. A similar comparison of the line shapes of $MoO_3,2H_2O$ and $(H_3O^+)HSO_4^-$ [18] also rules out the formulation $(H_3O^+)MoO_3(OH)^-$.

If the crystal had contained $H_4O^{2+}$ ions, a different line shape and second moment would have been expected, as can be shown by a calculation of what O–H distance would be required by the observed second moment. If we assume that the interaction between the groups of hydrogen atoms contributes 7·7 gauss$^2$ to the second moment, the contribution of the molecular groups themselves (the intramolecular second moment) whatever their nature is 23·0 gauss$^2$. As we have tried to show, this value is consistent with the presence of water molecules of an inter-proton distance of 1·56 Å. The exact relation between the

[14] Deeley and Richard, *Trans. Faraday Soc.*, 1954, **50**, 560.
[15] Gutowsky, Pake, and Bersohn, *J. Chem. Phys.*, 1954, **22**, 643.
[16] Ibers and Stevenson, Montreal Conference 1957; to be published in *J. Chem. Phys.* We are indebted to the authors for allowing us to see their paper before publication.
[17] Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., New York, 1945.
[18] Richards and Smith, *Trans. Faraday Soc.*, 1951, **47**, 1261; Itoh, Kusaka, Kiriyama, and Yabumoto, *J. Chem. Phys.*, 1953, **21**, 1895.
[19] Pringle, *Acta Cryst.*, 1954, **7**, 716; Ahmed and Cruickshank, *ibid.*, 1953, **6**, 385.

intramolecular second moment and the inter-proton distance $r_{jk}$ between the $j$th and $k$th proton for a rigid lattice is

$$\langle \Delta H^2 \rangle_{\text{intra}} = \frac{18\mu^2}{5N_s} \sum_{j>k} r_{jk}^{-6}$$

in which $N_s$ is the number of nuclei in the molecular grouping and $\mu$ is the magnetic moment of the proton in ergs gauss$^{-1}$. The most recent value for the nuclear magneton [20] being used, this equation becomes

$$\langle \Delta H^2 \rangle_{\text{intra}} = \frac{716{\cdot}16}{N_s} \sum_{j>k} r_{jk}^{-6}$$

in which $r_{jk}$ is in Å. If $N_s = 2$ and $\langle \Delta H^2 \rangle_{\text{intra}} = 23{\cdot}0$ gauss$^2$ $(= 4/5\alpha^2)$, then $r_{jk}$ comes to 1·58 Å. If $N_s = 4$ however, then for the same second moment (and a symmetrical $H_4O^{2+}$ ion being assumed), $r_{jk} = 1{\cdot}90$ Å, corresponding to an O–H distance of 1·16 Å. In water vapour $r_e$ is 0·958 Å, so that the O–H distance would have to expand by about 0·20 Å in forming $H_4O^{2+}$. In going from $NH_3$ to $NH_4^+$ (in $NH_4F$) the N–H distance expands by 0·027 Å from 1·014 to 1·041 Å [16,21] and an expansion of seven times this amount in the case of $H_4O^{2+}$ seems unlikely.

The infrared spectra of these hydrates provide some evidence for this view. The samples showed broad infrared absorption bands with maxima at the following frequencies (m medium, w weak, sh shoulder) (cm.$^{-1}$):

| | | | | | |
|---|---|---|---|---|---|
| $MoO_3,2H_2O$ ..... | 3100 m | 2336 w | 1592 m | 963 m | 909 m |
| $MoO_3,1{\cdot}1H_2O$ ..... | 3200 m | 2326 w | 1600 m | 1122 sh | 926 m |
| $MoO_3$ ..... | 2326 w | 1140 sh | 1081 sh | 980 m | 823 w |

The pairs of frequencies 3100, 1592 and 3200, 1600 cm.$^{-1}$ are absent from the spectrum of $MoO_3$ and are therefore attributed to water frequencies characteristic of the hydrated crystals. (Potassium chloride pellets prepared under anhydrous conditions show weak lines at 3425, 2936, and 1616 cm.$^{-1}$,[22] but lines of these frequencies could not be detected in the spectrum of $MoO_3$.) The lines at 1592 and 1600 cm.$^{-1}$ in the dihydrate and monohydrate respectively are attributed to an O–H bending frequency and are little changed from the value in water vapour of 1600 cm.$^{-1}$. The maxima at 3100 and 3200 cm.$^{-1}$ are attributed to the stretching frequencies and are considerably removed from the values in water vapour of 3652 ($\nu_2$) and 3756 ($\nu_3$). Such shifts are well known to occur in hydrogen-bonded compounds and there is a general tendency for the O–H stretching frequency to decrease with a shortening of the O–H . . . O distance. From the values listed by Nakamoto, Margoshes, and Rundle [23] one would expect an O–H . . . O distance in the hydrates of $MoO_3$ of between 2·73 and 2·75 Å. If these hydrogen bonds linked oxygen atoms at least one of which were attached to molybdenum, the grouping Mo–O . . . H–O would produce a contribution to $\beta^2$ because of the nuclear moment of $^{95}$Mo and $^{97}$Mo which together are in about 25% abundance. Calculation shows this to be at least one hundred times smaller than the actual values of $\beta^2$ required to give a reasonable theoretical curve. This again suggests that the fairly large values of $\beta^2$ are due to close approach of the water molecules to each other.

The nuclear magnetic resonance results give us only the inter-proton distance (1·56 ± 0·03 Å) in the water molecule; the O–H distance is not derived until we know the HOH angle. However, if we assume that this angle is the same as that in water vapour (104° 28′), the proton resonance results give an O–H distance of 0·99 Å, which is very close

[20] Cohen, Dumond, and Rollett, *Rev. Mod. Phys.*, 1955, **27**, 363.
[21] Drain, *Discuss. Faraday Soc.*, 1955, **19**, 200.
[22] Lucchesi and Glasson, *J. Amer. Chem. Soc.*, 1956, **78**, 1347.
[23] Nakamoto, Margoshes, and Rundle, *J. Amer. Chem. Soc.*, 1955, **77**, 6480.

to the value of 0·98 Å suggested by the data assembled in ref. 23. If the O–H distance were 1·16 Å, the predicted frequency would be around 1900 cm.$^{-1}$, which is not observed.

One of us (S. M.) thanks the Institute of Physics " Rudjer Bošković," Zagreb, Jugoslavia, for a research grant. We are indebted to Dr. I. Lindqvist for suggesting this problem, and to Professor E. G. Cox for his interest.

DEPARTMENT OF INORGANIC AND STRUCTURAL CHEMISTRY,
THE UNIVERSITY OF LEEDS. [*Received, September 25th,* 1957.]

---

## 172. *The Relative Stabilising Influences of Substituents on Free Alkyl Radicals. Part IV.*[1] *Selective Hydrogen-abstraction by Free* tert.-*Butoxy-radicals.*

By R. L. HUANG and SURINDER SINGH.

In the reaction of *tert.*-butoxy-radicals with compounds X·$CH_2$·$CH_2$·Y (X = Ph; Y = $CO_2$Et, COMe, COPh, $CO_2$H, CN, Cl, and *p*-Cl·$C_6H_4$) a 50% or higher yield of the " dimer " [·CHX·$CH_2$Y]$_2$ was obtained in the first three cases, indicating that hydrogen abstraction occurred selectively to give the radical ·CHX·$CH_2$Y and hence that X is more stabilising than Y on the intermediate alkyl radical (*i.e.*, Ph > $CO_2$Et, COMe, or COPh). In the other cases, the yields of " dimers " were small, rendering comparison impracticable.

A CHARACTERISTIC reaction of free alkyl or alkoxy-radicals in solution is the abstraction of hydrogen atoms from the hydrocarbon chain of the solvent. This occurs particularly readily when the solvent molecule contains a substituent group capable of stabilising, by resonance, the radical so produced. Action of the attacking radical then becomes highly specific, and hydrogen abstraction occurs invariably from the carbon atom adjacent to such a substituent, which may be phenyl, carbonyl, or other unsaturated group; the fate of the radical is usually dimerisation.[2,3] Examples are ethylbenzene and butanone, which with free methyl [2] or *tert.*-butoxy-radicals [3] give, *via* the radicals (I) and (III), the diphenylbutane (II) and the 1 : 4-diketone (IV), respectively:

$$R\cdot + Ph\cdot CH_2Me \longrightarrow RH + Ph\cdot CHMe\cdot \ (I);\ 2(I) \longrightarrow (CHPhMe)_2 \ (II)$$
$$R\cdot + Me\cdot CO\cdot CH_2Me \longrightarrow RH + Me\cdot CO\cdot CHMe\cdot \ (III);\ 2(III) \longrightarrow (CHMe\cdot COMe)_2 \ (IV)$$

In a substance X·$CH_2$·$CH_2$·Y in which both X and Y are unsaturated groups, both methylene groups would be open to attack by the free radical and, provided that there is no orientating effect of steric origin, the course of the reaction would be governed by the relative stability of the intermediate radical.[4] Thus, the radical ·CHX·$CH_2$Y would be formed in preference to X·$CH_2$·CHY· if X stabilises the intermediate alkyl radical more effectively than Y. Selective hydrogen-abstraction by a radical, the course of which can be unambiguously established by identification of the dimeric product, therefore provides a means by which the relative stabilising influences of X and Y can be compared. In this work we have studied the selective hydrogen-abstraction by *tert.*-butoxy-radicals (generated from *tert.*-butyl peroxide by thermolysis) of seven substances of the type indicated above, in which X is Ph and Y is $CO_2$Et, $CO_2$H, CN, Cl, COMe, COPh, or *p*-Cl·$C_6H_4$. A yield of 50% or higher of the " dimer " (·CHX·$CH_2$Y)$_2$ was obtained when Y was $CO_2$Et,

[1] Part III, Huang and Si-Hoe, *J.*, 1957, 3988.
[2] Kharasch, McBay, and Urry, *J. Org. Chem.*, 1945, **10**, (*a*) 394, (*b*) 401; (*c*) *J. Amer. Chem. Soc.*, 1948, **70**, 1269.
[3] (*a*) Farmer and Moore, *J.*, 1951, 131; (*b*) Moore, *J.*, 1951, 236; Huang and Kum-Tatt, *J.*, (*c*) 1954, 2570; (*d*) 1955, 4229.
[4] See Huang, *J.*, 1954, 3084.

COMe, and COPh, providing conclusive evidence for the greater stabilising effect of the phenyl group over these substituents. In the other cases, only small yields of dimeric products were obtained and no comparison could be made.

Reaction of ethyl β-phenylpropionate with *tert.*-butyl peroxide at 120° gave a 50% yield of diethyl *meso*-ββ′-diphenyladipate (V), which on hydrolysis furnished the *meso*-acid. The *meso*- and the racemic forms of the acid and the methyl ester, as well as the ethyl *meso*-ester, are known and their structures have received further confirmation by the conversion of the acids into chrysene derivatives.[5] The preferential formation of one stereomodification by the above radical reaction, though uncommon, has analogies in the dimerisation of the radicals derived from dimethyl succinate [2b] and *p*-methoxyphenylacetic acid,[3d] and is explicable in terms of the conformational aspects of the system concerned. Thus in the *meso*-adipate above, the gauche repulsions in the most favoured staggered conformation are Ph : $CH_2{\cdot}CO_2Et$, whereas in the diastereoisomer they are Ph : Ph and $CH_2{\cdot}CO_2Et$ : $CH_2{\cdot}CO_2Et$.[6] Hydrogen abstraction by *tert.*-butoxy-radicals from ethyl β-phenylpropionate therefore occurred with preferential formation of the radical (VI), rather than (VII), and it follows that the phenyl group is more stabilising than ethoxycarbonyl, confirming the results found in Part I [7] concerning these substituents.

β-Phenylpropionic acid by contrast gave a poor yield of *meso*-diphenyladipic acid, together with much polymeric material. No conclusion can be drawn concerning the phenyl and the carboxyl group.

β-Phenylpropionitrile by the same treatment afforded, also in modest yields, two isomers, m. p. 215° and 165°, and large quantities of polymers. The higher-melting isomer, obtained in higher yield, was very probably the (*meso*-)adiponitrile [8] (VIII), m. p. 212°. The lower-melting isomer was probably the previously unknown racemic form, or possibly the succinonitrile (IX). Again, on account of the low yields, no comparison of the substituent groups could be made.

$(\cdot CHPh{\cdot}CH_2{\cdot}CO_2Et)_2$ (V) $\quad \cdot CHPh{\cdot}CH_2{\cdot}CO_2Et$ (VI) $\quad Ph{\cdot}CH_2{\cdot}\dot{C}H{\cdot}CO_2Et$ (VII) $\quad (\cdot CHPh{\cdot}CH_2{\cdot}CN)_2$ (VIII)

$(CH_2Ph{\cdot}\dot{C}H{\cdot}CN)_2$ (IX) $\quad (\cdot CHPh{\cdot}CH_2{\cdot}COMe)_2$ (X) $\quad (\cdot CHPh{\cdot}CH_2{\cdot}COPh)_2$ (XI) $\quad \cdot CHPh{\cdot}CH_2{\cdot}CO{\cdot}Ph$ (XII)

$(\cdot CHPh{\cdot}CH_2Cl)_2$ (XIII) $\quad (\cdot CHAr{\cdot}CH_2Ph)_2$ (XIV): Ar = Ph (XVI): Ar = p-Cl·$C_6H_4$ $\quad (\cdot CPh{:}CH{\cdot}Ph)_2$ (XV)

From 4-phenylbutan-2-one and *tert.*-butyl peroxide was obtained, in a 57% yield, the 1 : 6-diketone (X) which Dippy and Lewis [9] had prepared, in one stereomodification only, by an unambiguous method. The phenyl group thus has a greater stabilising influence than an isolated ketonic group (acetyl). This is the first direct comparison of these substituents, and the result is in agreement with the relation deduced for them in Part II.[10]

β-Phenylpropiophenone gave, by the same reaction, the *meso*-form of the diketone (XI), which had previously been synthesised, in both the *meso*- and the racemic form, from benzylideneacetophenone by reduction [11] and by a cobaltous chloride-catalysed Grignard reaction,[12] and from ββ′-diphenyladipoyl dichloride and diphenylcadmium.[11] Although the yield of the diketone (XI) in the radical reaction was low, the high recovery of the

[5] Oommen and Vogel, *J.*, 1930, 2148; Ramage and Robinson, *J.*, 1933, 607; Wilds and Sutton, *J. Org. Chem.*, 1951, **16**, 1371.

[6] Cf. Newman: "Steric Effects in Organic Chemistry," Wiley & Sons, New York, 1956, p. 147. We thank a Referee for drawing our attention to this point.

[7] Huang, *J.*, 1956, 1749.

[8] Baker and Lapworth, *J.*, 1924, 2333.

[9] Dippy and Lewis, *Rec. Trav. chim.*, 1937, **56**, 1000.

[10] Huang, *J.*, 1957, 1342.

[11] Finch and White, *J.*, 1950, 3367.

[12] Kharasch and Sayles, *J. Amer. Chem. Soc.*, 1942, **64**, 2972.

starting material, together with the fact that little or no by-product was formed, leaves little doubt that the main course of the reaction was the generation of the radical (XII), indicating that the benzene ring is more stabilising than the benzoyl group. This has been confirmed in a study of the selective bromination by *N*-bromosuccinimide.[13]

In an attempt to compare the phenyl group with the chlorine atom, phenethyl chloride was treated with *tert.*-butyl peroxide in the usual manner. Only a 16% yield was obtained of a substance which may have structure (XIII), but no degradative studies were carried out. Another attempt to compare these substituents was made by the homolytic addition of bromotrichloromethane to ω-chlorostyrene, as described in Part I.[7] This gave mainly polymeric products, together with some 1 : 1 adduct which could not be purified.

The relative stabilising influences are thus: Ph > $CO_2Et$, COMe, COPh.

By using substituted dibenzyls, this method could be extended to a comparison of the stabilising effects of aryl groups, and thus provide a parallel approach to that involving the cleavage of dibenzyl ethers (Part III [1]). Dimerisation of the radical derived from a dibenzyl would give a 1 : 2 : 3 : 4-tetra-arylbutane which, if unknown, could be identified by degradation, for example, by bromination followed by dehydrobromination and oxidation. A case studied was that of 4-chlorodibenzyl, in a comparison of the stabilising capacities of the phenyl and the *p*-chlorophenyl group. As a model experiment, dibenzyl itself was treated with *tert.*-butyl peroxide; it gave a 38% yield of the tetraphenylbutane [14] (XIV). Model degradations were then carried out on this tetraphenyl homologue. *N*-Bromosuccinimide under various conditions led to three dibromo-derivatives, m. p. 163°, 181°, and 201°. The highest-melting isomer (obtained in a 35% yield), on dehydrobromination with dimethylaniline, afforded only small quantities of the known tetraphenylbutadiene (XV), while the isomer of m. p. 181° (42% yield) gave only intractable oils; the third isomer being obtained in low yields was not degraded. It appears therefore that degradation of unknown tetra-arylbutanes by this route (bromination, dehydrobromination, then oxidation) is not promising. Further, when 4-chlorodibenzyl reacted with *tert.*-butyl peroxide, only traces of a tetra-arylbutane, presumably (XVI) (since *p*-chlorophenyl has been found to be more stabilising on alkyl radicals than phenyl [1]), were formed, together with polymeric products. This project was therefore abandoned.

## Experimental

Unless otherwise stated, experiments with *tert.*-butyl peroxide were carried out under nitrogen in a sealed tube heated at 120° for 48 hr., 0·5 mole of the peroxide being used per mole of the substance studied.

*Ethyl β-Phenylpropionate.*—The ester (15 g., 0·084 mole; b. p. 72°/1 mm., $n_D^{24}$ 1·4930) and *tert.*-butyl peroxide (8·6 g., 0·058 mole) after 48 hr. at 120° gave, on distillation, (i) volatile material, (ii) unchanged ester (7·4 g.), and (iii) a viscous liquid (7·6 g.). A portion of this (1·2 g.) was evaporatively distilled, giving three fractions (bath-temp., *ca.* 200°/0·5 mm.) all crystallising and affording diethyl *meso*-ββ′-diphenyladipate (0·6 g.), needles (from ethanol), m. p. 113° (Found: C, 74·9; H, 7·4. Calc. for $C_{22}H_{26}O_4$: C, 74·6; H, 7·3%). There was an undistillable residue (0·6 g.). The adipate on hydrolysis with aqueous ethanolic potassium hydroxide gave the acid, needles (from ethanol), m. p. 269°. Oommen and Vogel [5] record m. p.s 114° and 270—271°, respectively.

*β-Phenylpropionic Acid.*—The product from this acid (10 g.) and *tert.*-butyl peroxide, after removal of volatile fractions and unchanged acid (b. p. 110—114°/0·7 mm.; 5·2 g.), gave on treatment with ether small quantities of *meso*-ββ′-diphenyladipic acid, m. p. and mixed m. p. 269° (*ca.* 0·15 g.), no other crystalline material being isolated. The bulk of the product was then esterified with ethanol (sulphuric acid) and evaporatively distilled, giving three fractions (bath at 170°, 210—220° and 240—250° respectively, at 0·7 mm.), none of which crystallised. When heated with the peroxide at 90° for 6 days, β-phenylpropionic acid (10 g.) gave unchanged material (7·8 g.), the above adipic acid (0·35 g.), and intractable oils.

[13] Huang and Williams, unpublished work.
[14] Smith and Hoehn, *J. Amer. Chem. Soc.*, 1941, **63**, 1184.

XUM

β-*Phenylpropionitrile.*—The nitrile was prepared (*a*) by dehydration of the amide with phosphoric anhydride at 130—150° for 40 min., followed by extraction with benzene (57% yield) and (*b*) by benzylation of acetonitrile [15] by sodamide and benzyl chloride (20% yield). It had b. p. 74—76°/1 mm., $n_D^{22}$ 1·5220 (Found: C, 82·7; H, 6·9. Calc. for $C_9H_9N$: C, 82·45; H, 6·9%). The product from this nitrile (11·0 g.) and the peroxide, after recovery of unchanged nitrile (5·4 g.) by distillation, was dissolved in benzene and adsorbed on alumina, and eluted by benzene followed by benzene–acetone (20 : 1), to give the following: (*a*) ββ′-diphenyladiponitrile, which crystallised from benzene in needles, m. p. 215° (0·25 g.) (Found: C, 83·1; H, 6·2. Calc. for $C_{18}H_{16}N_2$: C, 83·1; H, 6·15%); (*b*) an *isomer*, prisms (from benzene), m. p. 165° (0·10 g.) (Found: C, 83·25; H, 6·1. $C_{18}H_{16}N_2$ requires C, 83·1; H, 6·15%); and (*c*) intractable oils which appeared polymeric. Baker and Lapworth [8] report m. p. 212° for the adiponitrile. When the proportion of the peroxide was increased (to 1 : 1), there was a 20% recovery of nitrile and a small yield of the above adiponitrile of m. p. 215°, together with large quantities of polymer.

4-*Phenylbutan-2-one.*—The mixture from 4-phenylbutan-2-one (8·0 g.; prepared from ethyl α-benzylacetoacetate,[16] b. p. 66—68°/1 mm., $n_D^{22}$ 1·5109) and *tert.*-butyl peroxide on cooling deposited 4 : 5-diphenyloctane-2 : 7-dione (0·7 g.) which was filtered off and after two recrystallisations from methanol melted at 160° (Found: C, 81·0; H, 7·5. Calc. for $C_{20}H_{22}O_2$: C, 81·6; H, 7·5%) (Dippy and Lewis [9] report m. p. 161°). The filtrate was distilled, giving volatile material, unchanged ketone (3·6 g.), and a viscous residue (3·7 g.). This residue on evaporative distillation afforded a fraction, b. p. 170—180° (bath)/0·7 mm., which in contact with methanol crystallised to give more of the dione, m. p. 160° (1·9 g.). The dione (0·13 g.), when refluxed with hydroxylamine hydrochloride (0·6 g.) in pyridine (4 c.c.) and ethanol (20 c.c.) for 4·5 hr., furnished the dioxime, m. p. 232° (from ethanol). Harries and Eschenbach [17] report m. p. 235—237°.

β-*Phenylpropiophenone.*—The mixture from this ketone (15 g.; m. p. 72°; prepared from benzylideneacetophenone by hydrogenation) and the peroxide was extracted with boiling ethanol. The solid which survived extraction was *meso*-1 : 3 : 4 : 6-tetraphenylhexane-1 : 6-dione (0·57 g.) and crystallised from benzene as needles, m. p. 269°, alone or mixed with a sample prepared by Finch and White's method [11] (Found: C, 86·6; H, 6·3. Calc. for $C_{30}H_{26}O_2$: C, 86·1; H, 6·2%) (lit., m. p. 269°,[11] 276° [12]). The ethanolic extract was concentrated in stages, and the solids which separated were collected, giving five crops of unchanged ketone (11·5 g.). Small quantities of a brown oil accompanied the fifth crop.

In another experiment in which more peroxide was used (1 : 1), β-phenylpropiophenone (18 g.) gave (after chromatography on alumina): unchanged ketone (4·1 g.), the 1 : 6-dione (0·4 g.), and polymer (13·6 g.).

*Phenethyl Chloride.*—The product from this chloride [18] (9·1 g.; b. p. 34°/1 mm., $n_D^{22}$ 1·5285) and *tert.*-butyl peroxide, after removal of volatile material and unchanged chloride (5·0 g.), was a viscous liquid (4·1 g.) which in contact with benzene deposited crystals, probably 1 : 4-*dichloro*-2 : 3-*diphenylbutane*, m. p. 140—150° (0·4 g.) raised to 180° on recrystallisation from the same solvent from which it separated in stout needles (Found: C, 69·0; H, 5·7. $C_{16}H_{16}Cl_2$ requires C, 68·8; H, 5·7%). Chromatography of the filtrate yielded a further crop of the butane (0·26 g.). With less peroxide (10·4 g.) the same chloride (40 g.) after 24 hours' heating gave much unchanged material (32 g.) and a 13% yield of the butane derivative (m. p. 180°).

*Dibenzyl.*—The product from dibenzyl (10·0 g.) and *tert.*-butyl peroxide after removal, by distillation, of volatile material and unchanged dibenzyl (b. p. 82—84/0·5 mm.; 4·4 g.), gave a viscous liquid (5·6 g.) which, on dissolution in benzene–*cyclo*hexane and storage, deposited 1 : 2 : 3 : 4-tetraphenylbutane (2·1 g.). This crystallised from the above solvent mixture in needles, m. p. 179° (Found: C, 92·6; H, 7·2. Calc. for $C_{28}H_{26}$: C, 92·8; H, 7·2%). Smith and Hoehn [14] report m. p. 179—180°. The yield of tetraphenylbutane dropped when more peroxide was used.

*Wohl–Ziegler Bromination of* 1 : 2 : 3 : 4-*Tetraphenylbutane.*—The butane (0·5 g.) and *N*-bromosuccinimide in pure carbon tetrachloride (20 c.c.) were irradiated with a 100 w incandescent lamp under nitrogen until reaction was complete (30—40 min.). Succinimide

[15] Chen and Barthel, *J. Amer. Chem. Soc.*, 1953, **75**, 4287.
[16] Bergström and Agostinho, *ibid.*, 1945, **67**, 2152.
[17] Harries and Eschenbach, *Ber.*, 1896, **29**, 380.
[18] Norris and Taylor, *J. Amer. Chem. Soc.*, 1924, **46**, 753.

was filtered off and the filtrate concentrated under partially reduced pressure, and the dibromo-compound which separated crystallised from *cyclo*hexane. Four such bromination experiments were carried out, as summarised in the annexed Table.

| Mole of *N*-bromosuccimide used per mole of hydrocarbon | Irradiation (min.) | M. p. of dibromide obtained | Yield (%) | Found (%) * C | H | Br |
|---|---|---|---|---|---|---|
| 1·5 | 30 | 181° | 24 | 65·1 | 4·6 | — |
| 2 | 30 | 162—163, | 36 | — | — | 30·0 |
| | | 181 | 1 | — | — | — |
| 3 | 40 | 181 | 42 | — | — | — |
| 3 | 40 | 201 | 35 | — | — | 30·4 |

* $C_{28}H_{24}Br_2$ requires C, 64·6; H, 4·6; Br, 30·8%.

*Dehydrobromination.* The dibromide of m. p. 201° (0·3 g.) was refluxed with dimethylaniline for 15 min. under nitrogen. The mixture was poured into an excess of dilute hydrochloric acid, and the product taken up in ether, washed with aqueous sodium hydrogen carbonate, dried, and concentrated, to give small quantities of, probably, 1 : 2 : 3 : 4-tetraphenylbuta-1 : 3-diene which after one crystallisation from light petroleum had m. p. 177° (needles). Smith and Hoehn [14] record m. p. 182·5—183°. The dibromide of m. p. 181° on similar treatment gave an oil.

*4-Chlorodibenzyl.*—The mixture from 4-chlorodibenzyl [19] (25 g., m. p. 49°) and the peroxide in contact with light petroleum deposited, probably, 2 : 3-*di*-p-*chlorophenyl*-1 : 4-*diphenylbutane*, which was filtered off and crystallised from benzene in needles, m. p. 191° (0·12 g.) (Found: C, 77·8; H, 5·7. $C_{28}H_{24}Cl_2$ requires C, 77·9; H, 5·6%). The filtrate was concentrated, then adsorbed on alumina, and eluted with light petroleum, then light petroleum–benzene (35 fractions being collected), to give unchanged dibenzyl (10·5 g.), traces of the above butane, and intractable oils.

Microanalyses by Dr. W. Zimmermann, Melbourne.

UNIVERSITY OF MALAYA, SINGAPORE. [*Received, October 14th*, 1957.]

[19] Bergman, Weizmann, and Shapiro, *J. Org. Chem.*, 1944, **9**, 408.

## 173. *The Tautomerism and Steric Properties of 9-Substituted Phenanthridines.*

By C. B. REESE.

The amino-form (IIa) of 9-aminophenanthridine has been found to predominate in aqueous-ethanolic solution. The tautomeric equilibrium of the isomeric 5-aminoacridine (I) is considered in comparison. The ultraviolet absorption spectra of the methiodides of 9-amino-, 9-methylamino-, and 9-dimethylamino-phenanthridine have been examined. Phenanthridone (VII) has been shown to adopt the lactam form in ethanol.

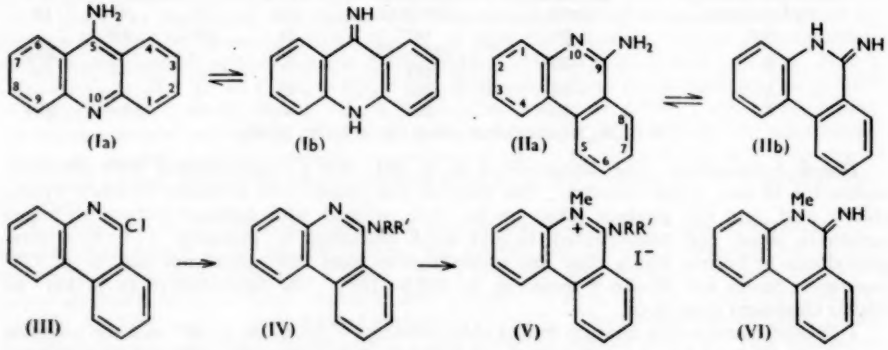
ALBERT and his colleagues [1] determined the base-strengths of 5-aminoacridine (I) and some of its *N*-alkyl derivatives. Short [2] examined its infrared spectrum in chloroform solution and concluded that the imino-form (Ib) made no contribution in this solvent. Ultraviolet absorption spectra of these compounds have also been examined.[3] As these results seemed inconclusive, it was decided to investigate the tautomerism of the related isomer, 9-aminophenanthridine (II). Morgan and Walls [4] commented on this problem when they prepared this compound, but no detailed investigation ensued.

9-Chlorophenanthridine (III), prepared by the action of phosphoryl chloride on phenanthridone [5] (VII), reacted readily with ammonia, methylamine, and dimethylamine, yielding 9-amino- (IV; R = R′ = H), 9-methylamino- [6] (IV; R = H, R′ = Me), and

[1] Albert in Elderfield's "Heterocyclic Compounds," Wiley, New York, 1952, Vol. IV, p. 491 *et seq.*
[2] Short, *J.*, 1952, 4584.
[3] Craig and Short, *J.*, 1945, 419; Acheson, Burstall, Jefford, and Sanson, *J.*, 1954, 3742.
[4] Morgan and Walls, *J.*, 1932, 2225.
[5] Badger, Seidler, and Thomson, *J.*, 1951, 3207.
[6] Morgan and Walls, *J.*, 1938, 389.

XUM

9-dimethylamino-phenanthridine (IV; R = R′ = Me) respectively. These three compounds reacted at position 10 with methyl iodide to yield the corresponding methiodides (V). 9 : 10-Dihydro-9-imino-10-methylphenanthridine (VI) was obtained when 9-amino-10-methylphenanthridinium iodide (V; R = R′ = H) was treated with alkali.




In order to determine the tautomerism constant of 9-aminophenanthridine, its base-strength and those of three of its *N*-methyl derivatives were measured. As these compounds were sparingly soluble in water, their p$K_a$'s were determined, in ~M/400-concentration, in 70% ethanol at 20°. The values were: 9-amino- 6·30, 9-methylamino- 6·70, and 9-dimethylamino-phenanthridine 4·91; and compound (VI) 9·10.

The p$K_a$ of 9-aminophenanthridine had previously been found [7] to be 7·31 in water and 6·75 in 50% ethanol. Thus our value obtained in 70% ethanol was approximately one unit less than the true value. It should be emphasized that our p$K_a$ values are not absolute and their significance lies in the differences.

Angyal and Angyal [8] have used the p$K_a$ values of heterocyclic bases to determine tautomeric equilibrium constants. This method has now been applied to 9-aminophenanthridine. However, owing to the possible introduction of steric hindrance, it was necessary to apply with extreme care the well-substantiated approximation [8-10] that *N*-methylation of compounds of this type changes their p$K_a$'s only slightly. It was assumed that the p$K_a$ of the non-tautomeric 9 : 10-dihydro-9-imino-10-methylphenanthridine (VI) did not differ appreciably from that of the imino-form of 9-aminophenanthridine (IIb). The observed similarity between the ultraviolet absorption spectra of compound (VI) and 9-aminophenanthridine in acid solution (Fig. 1) indicated that methylation at position 10 of the conjugate acid of the latter compound did not introduce steric hindrance and thus change its chromophore considerably.

As 9 : 10-dihydro-9-imino-10-methylphenanthridine (VI) was found to be a much stronger base than 9-aminophenanthridine, it was concluded that the imino-form (IIb) did not contribute greatly to the structure of the latter in 70% ethanol. From the p$K_a$ values the tautomerism constant $6·3 \times 10^2$ was calculated, indicating that the amino-form had a greater stability than the imino-form by 3·9 kcal./mole.

It is noteworthy that 9-dimethylaminophenanthridine is a much weaker base than 9-amino- or 9-methylamino-phenanthridine. Steric interaction between the two *N*-methyl groups and the 8-hydrogen atom probably prevents the first compound from adopting a planar configuration and thus partially localizes the lone-pair of electrons on the exocyclic nitrogen atom. This interpretation is substantiated by the difference (see Fig. 1) between

[7] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[8] Angyal and Angyal, *J.*, 1952, 1461.
[9] Kenner, Reese, and Todd, *J.*, 1955, 855; Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.
[10] Albert and Goldacre, *J.*, 1946, 706.

the ultraviolet absorption spectrum of the conjugate acid of 9-dimethylaminophenanthridine and those of 9-aminophenanthridine and 9 : 10-dihydro-9-imino-10-methylphenanthridine (VI). Evidently one methyl group on either the 9-amino-group or the 10-nitrogen atom is insufficient to distort the planarity of the molecule.

The structures allotted to the methiodides accord with the facts that action of alkali on the first yields compound (VI), and hydrolysis of the third [6] yields 10-methylphenanthridone (VIII). The evidence in favour of the structure of 9-methylaminophenanthridine methiodide is that its ultraviolet spectrum (Fig. 2, curve *B*) differs from that of

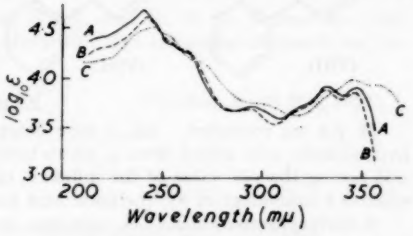



FIG. 1. *Ultraviolet absorption spectra in* 0·1N-*hydrochloric acid of* 9-*aminophenanthridine* (*A*; ——), 9 : 10-*dihydro*-9-*imino*-10-*methylphenanthridine* (*B*; – – – –), *and* 9-*dimethylaminophenanthridine* (*C*; . . . .).

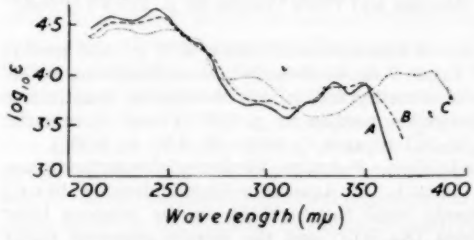



FIG. 2. *Ultraviolet absorption spectra in* 95% *ethanol of* 9-*amino*- (*A*; ——), 9-*methylamino*- (*B*; – – – –) *and* 9-*dimethylamino*-10-*methylphenanthridinium iodide* (*C*; . . . .).

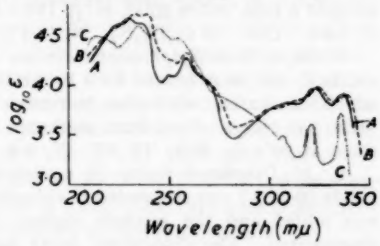



FIG. 3. *Ultraviolet absorption spectra in* 95% *ethanol of phenanthridone* (*A*; ——), 10-*methylphenanthridone* (*B*; – – – –), *and* 9-*methoxyphenanthridine* (*C*; . . . .).

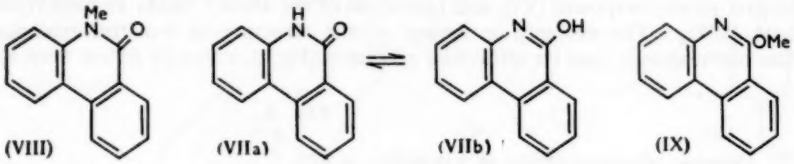
9-dimethylaminophenanthridine in acid solution (Fig. 1, curve *C*). If the chromophore of the conjugate acid of 9-aminophenanthridine (Fig. 1, curve *A*) is taken to be that of a planar cation, it is unlikely that 9-dimethylaminophenanthridine methiodide (Fig. 2, curve *C*) has a planar cation. This is possibly also true, to a smaller extent, for 9-methylaminophenanthridine methiodide (Fig. 2, curve *B*). The resemblance between curve *C* of Fig. 1 and curve *C* of Fig. 2 suggests that 9-dimethylamino-, as well as 9-amino- and 9-methylamino-phenanthridine, is protonated on position 10. The spectroscopic evidence confirms what is expected from models of these compounds. It is not possible to make a planar model of 9-dimethylaminophenanthridine, its methiodide, or 9-methylaminophenanthridine methiodide.

The $pK_a$ results [10,11] for derivatives of 5-aminoacridine (I) followed the same general pattern as for the corresponding derivatives of 9-aminophenanthridine (II). However, in the case of 5-aminoacridine the result was less definite and it was possible that the two tautomeric forms (Ia and Ib) had similar stabilities. Acheson *et al.*[3] recently used ultraviolet spectroscopic evidence to support the prevalence of the imino-form (Ib) in certain solutions, but their argument was invalidated by the introduction of a steric factor in a model compound.[12]

The ultraviolet absorption spectrum, in 95% ethanol, of phenanthridone (VII) (Fig. 3, curve *A*) resembles that of 10-methylphenanthridone (VIII) (curve *B*) but is quite unlike that of 9-methoxyphenanthridine (IX) (curve *C*). Therefore, it seems probable that

[11] Albert and Goldacre, *J.*, 1943, 454.
[11] Albert, Chem. Soc. Special Publ. No. 3, 1955, p. 130.

phenanthridone exists almost exclusively in the lactam (VIIa) rather than the lactim form (VIIb) in ethanol. Albert and Phillips [13] reached the same conclusion from $pK_a$ studies. This result is expected as the energy difference of 3·9 kcal./mole between the two tautomers of 9-aminophenanthridine is much less than the difference in stability between a lactam and a lactim grouping.[14]




(VIII) (VIIa) (VIIb) (IX)

## Experimental

M. p.s are corrected. $pK_a$'s were determined by plotting pH against the volume of 0·1N-hydrochloric acid added from a micro-burette to approximately M/400-solutions of the bases and noting the pH value of the inflexion of the curve. This was checked with the pH value when 0·5 equivalent of hydrochloric acid had been added.

*9-Aminophenanthridine.*—A mixture of 9-chlorophenanthridine (3 g.) and methanol, saturated with ammonia at 0° (8 c.c.), was heated for 5 hr. at 180°. The solvent was removed and the residue was extracted with dilute sulphuric acid. Crude 9-aminophenanthridine was precipitated when this extract was neutralized with aqueous sodium hydroxide. It recrystallized from aqueous ethanol as needles (1·6 g.). A small quantity was sublimed at 140°/0·5 mm. to yield a pale yellow solid, m. p. 193—195° (Morgan and Walls [4] record m. p. 195·5°) (Found: N, 14·8. Calc. for $C_{13}H_{10}N_2$: N, 14·4%).

*9-Amino-10-methylphenanthridinium Iodide.*—9-Aminophenanthridine (0·31 g.) and methyl iodide (1 c.c.) were heated for 4 hr. at 125°. Crude *9-amino-10-methylphenanthridinium iodide*, which was washed with ether to remove excess of methyl iodide, was obtained in quantitative yield. It recrystallized from methanol in fine yellow needles, m. p. 257° (Found, in material dried at 60°: C, 49·8; H, 3·7; N, 8·6. $C_{14}H_{13}N_2I$ requires C, 50·0; H, 3·9; N, 8·3%).

*9 : 10-Dihydro-9-imino-10-methylphenanthridine.*—9-Amino-10-methylphenanthridinium iodide (0·25 g.) was suspended in chloroform (50 c.c.). 3N-Aqueous sodium hydroxide (10 c.c.) was added and the mixture shaken vigorously until the turbidity in the aqueous layer disappeared. The chloroform layer was dried ($Na_2SO_4$), and the solvent removed under reduced pressure to leave a brown gum. This was further dried by azeotropic distillation with benzene, and then recrystallized from this solvent as a discoloured solid (0·065 g.). This crude *9 : 10-dihydro-9-imino-10-methylphenanthridine* was purified by " cold-finger " distillation at 110°/0·5 mm. to give a colourless crystalline solid, m. p. 92° (Found: C, 80·7; H, 5·6; N, 13·5. $C_{14}H_{12}N_2$ requires C, 80·8; H, 5·8; N, 13·5%).

*9-Methylaminophenanthridine.*—This was prepared by the method of Morgan and Walls. The purified material had m. p. 187—188° (Morgan and Walls [7] record m. p. 187°) (Found: N, 13·7. Calc. for $C_{14}H_{12}N_2$: N, 13·5%).

*9-Dimethylaminophenanthridine.*—9-Chlorophenanthridine (1 g.) was heated with pure anhydrous dimethylamine (about 2 g.) for 2 hr. at 100°. The excess of dimethylamine was allowed to evaporate and the residue was extracted with benzene. The solvent was removed under reduced pressure to leave a brown gum in quantitative yield. This gum, recrystallized from light petroleum (b. p. 60—80°) and finally purified by " cold-finger " distillation at 110°/0·5 mm., gave 9-dimethylaminophenanthridine, m. p. 60° (Morgan and Walls [7] record m. p. 61·5°).

*10-Methyl-9-methylaminophenanthridinium Iodide* 9-Methylaminophenanthridine (0·31 g.) was quaternized with excess of methyl iodide in the same manner as above. The *methiodide hemihydrate* crystallized from methanol in pale yellow needles, m. p. 223—224° with darkening and effervescence (Found, in material before and after being dried at 100°: C, 50·1; H, 4·6; N, 8·1. $C_{15}H_{15}N_2I,\frac{1}{2}H_2O$ requires C, 50·1; H, 4·5; N, 7·8%).

*9-Dimethylamino-10-methylphenanthridinium Iodide.*—This was prepared from 9-dimethylaminophenanthridine in a similar manner. It had m. p. 222° (decomp.) (Morgan and Walls [7]

[13] Albert and Phillips, *J.*, 1956, 1294.
[14] Branch and Calvin, " The Theory of Organic Chemistry," Prentice-Hall, New York, 1941, p. 289.

XUM

give m. p. 230°) (Found, in material dried at 80°: C, 52·6; H, 4·8. Calc. for $C_{16}H_{17}N_2I$: C, 52·7; H, 4·7%).

*9-Methoxyphenanthridine.*—9-Chlorophenanthridine (0·21 g.) in anhydrous methanol (30 c.c.) was treated with a solution of sodium methoxide [from sodium (0·1 g.) and methanol (8 c.c.)] and refluxed for ½ hr., after which the solvent was removed. A benzene extract of the residue was evaporated to pale yellow crystals of 9-methoxyphenanthridine in quantitative yield. A colourless crystalline solid, m. p. 52°, was obtained by a " cold-finger " distillation of the crude product at 108°/1·0 mm. (Found: C, 80·4; H, 5·2; N, 6·6. Calc. for $C_{14}H_{11}ON$: C, 80·4; H, 5·3; N, 6·7%).

The author thanks Professor Sir Alexander Todd, F.R.S., and Dr. G. W. Kenner for their continued interest of advice, and the Department of Scientific and Industrial Research for the award of a maintenance allowance.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 26th,* 1957.]

---

# NOTES.

## 174. *The Reaction of 9-Chlorophenanthridine and Related Compounds with Tertiary Amines.*

By C. B. REESE.

An attempt was made to quaternize 9-chlorophenanthridine (I) with excess of trimethylamine to obtain trimethyl-9-phenanthridinylammonium chloride (II), so that its ultraviolet absorption spectrum could be compared with those of other quaternary phenanthridine derivatives.[1] Preparation of the quaternary salt, and isolation as the derived iodide, had been described by Morgan and Walls,[2] who supported the structure by an iodine analysis. However, attempts to repeat this experiment under the same conditions with ethanolic trimethylamine, or at the lower temperature of 120° with pure trimethylamine, yielded a crystalline iodide which has been shown to be tetramethylammonium iodide. Unfortunately, 9-chlorophenanthridine reacted at a negligible rate with trimethylamine at 37°, perhaps partly owing to its relative insolubility at this temperature.

As some difficulty had been encountered in obtaining the other product of this reaction in a pure state, the reaction between 9-chlorophenanthridine and the tertiary amine, 4-methylmorpholine was investigated. 9-Morpholinophenanthridine (III) and 4 : 4-dimethylmorpholinium chloride were obtained quantitatively.

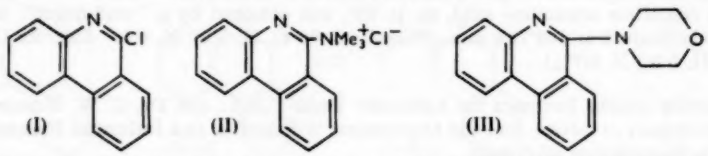
2-Chloroquinoline and 1-chloro*iso*quinoline were both reactive chloro-compounds, like 9-chlorophenanthridine. Further, the 1-position of *iso*quinoline was likely to be hindered to the same extent as the 9-position of phenanthridine. Both the compounds had the advantage of being freely soluble in trimethylamine at room temperature. When the former was heated with an excess of 4-methylmorpholine at 180°, 2-morpholinoquinoline and 4 : 4-dimethylmorpholinium chloride were the exclusive products. However, quaternization of 2-chloroquinoline with pure trimethylamine at 40°, followed by addition of iodide, gave trimethyl-2-quinolylammonium iodide in moderate yield. The structure of this compound was confirmed by alkaline hydrolysis to 2-quinolone. Therefore, at a lower temperature, it was possible to quaternize 2-chloroquinoline normally. The product obtained at a higher temperature may have been formed by reaction of quaternary compound with excess of amine.

1-Chloro*iso*quinoline with excess of 4-methylmorpholine at 180—200° gave 4 : 4-dimethylmorpholinium chloride as the only salt isolated. With an excess of pure trimethylamine at 35° (30 days) it afforded a very small quantity of water-soluble material, and tetramethylammonium iodide was obtained when the aqueous solution was treated with

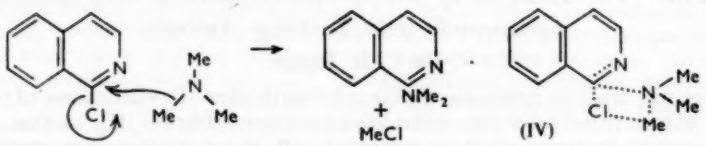
[1] Reese, preceding paper.
[2] Morgan and Walls, *J.*, 1938, 389.

iodide. Thus the normal quaternary compound was not even obtained at this low temperature.

There are, at least, two reasonable interpretations of this observation. One is that the normal quaternary product might be formed initially and be sufficiently reactive at 35° to methylate some of the excess of trimethylamine present. A second is that it might




be sterically impossible for the nitrogen atom of the bulky trimethylamine molecule to get within bonding distance of the 1-position of the *iso*quinoline nucleus. There is then the possibility of demethylation of the attacking trimethylamine by the departing chloride ion, to yield 1-dimethylamino*iso*quinoline and methyl chloride, which is then converted into tetramethylammonium chloride. This second mechanism is indicated in the annexed formulæ.




The transition state (IV) was at least as likely to regenerate the starting materials as it was to yield the products. No accurate rate measurements were made, but this reaction was noticeably slower than quaternization of 2-chloroquinoline under similar conditions. This was difficult to explain solely by electronic theory. If a steric factor operated in the case of 1-chloro*iso*quinoline, then it would be expected also to have done so in the case of 9-chlorophenanthridine (I).

*Experimental.*—M. p.s are corrected.

***Reaction between 9-chlorophenanthridine and trimethylamine.*** (*a*) 9-Chlorophenanthridine (1 g.) was heated with 33% alcoholic trimethylamine (2·5 c.c.) in a sealed tube at 160° for 4 hr. Adding an excess of aqueous potassium iodide to an aqueous extract of the products, gave colourless crystals (*ca.* 0·03 g.) which, recrystallized from methanol, did not melt below 350°. Their aqueous solution had no absorption maximum in the region 220—320 mμ and analysis corresponded to that of tetramethylammonium iodide (Found, in material dried at 80°: C, 24·1; H, 6·0; N, 6·8. Calc. for $C_4H_{12}NI$: C, 23·9; H, 6·0; N, 7·0%).

(*b*) 9-Chlorophenanthridine (0·5 g.) was heated with pure trimethylamine (*ca.* 4 g.) in a sealed tube at 120° for 10 hr. The excess of amine was allowed to evaporate at room temperature and the residue was washed with dry benzene. The colourless crystals which remained were converted into the iodide and purified as above (Found: C, 24·3; H, 6·3%).

(*c*) 9-Chlorophenanthridine (0·7 g.) was allowed to react with excess of trimethylamine (*ca.* 5 g.) at 37° for 14 days. The products were treated as above, but only *ca.* 0·001 g. of crystalline material remained after the benzene extraction. This was dissolved in water and had no absorption peak in the range 220—300 mμ.

***Reaction between 9-Chlorophenanthridine and 4-methylmorpholine.*** 9-Chlorophenanthridine (0·5 g.) was heated with an excess of 4-methylmorpholine (3 c.c.) at 200° for 5 hr. Crystals separated from the cooled products. Dry benzene (10 c.c.) was added to the mixture, which was then filtered. The residue recrystallized from ethanol–ethyl acetate as a colourless, extremely hygroscopic substance which decomposed above 330°, without melting. When treated with silver oxide, its aqueous solution gave a strongly alkaline reaction. Elementary analysis confirmed that this compound was 4 : *4-dimethylmorpholinium chloride* (Found, in material dried at 50°: C, 47·5; H, 8·8; N, 9·1. $C_6H_{14}ONCl$ requires C, 47·5; H, 9·2; N, 9·2%).

The filtrate (above) was evaporated to yield a semicrystalline gum, which was recrystallized

from ethanol as colourless plates, m. p. 92°. This was redistilled in a " cold-finger " apparatus at 110°/0·5 mm. to give *9-morpholinophenanthridine*, m. p. 94—96° (Found: C, 77·2; H, 6·2; N, 10·9. $C_{17}H_{16}ON_2$ requires C, 77·3; H, 6·1; N, 10·6%).

Both the crude products were obtained quantitatively.

*Reaction between 2-chloroquinoline and 4-methylmorpholine.* 2-Chloroquinoline (0·58 g.) was treated, in the same way, with excess of 4-methylmorpholine (3 c.c.) at 180° for 5 hr. The products were washed with dry benzene to leave a quantitative residue of 4 : 4-dimethylmorpholinium chloride (Found: C, 47·7; H, 9·3; N, 9·3%). The benzene washings, when evaporated, yielded crystals which, recrystallized from light petroleum (b. p. 40—60°) and resublimed (70°/0·5 mm.), gave *2-morpholinoquinoline*, m. p. 91° (Found: C, 72·8; H, 6·4; N, 13·2. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·5; N, 13·1%).

*Reaction between 2-chloroquinoline and trimethylamine at 40°.* 2-Chloroquinoline (3·2 g.) was allowed to react with a large excess of trimethylamine (*ca.* 10 g.) at 40° for 48 hr., crystals separating. The excess of trimethylamine was allowed to evaporate and benzene (20 c.c.) was added. The mixture was filtered and the residue was dissolved in water (2 c.c.). Saturated aqueous potassium iodide (1 c.c.) was then added. Crystals (0·21 g.) which were precipitated, when twice recrystallized from water, yielded cream-coloured plates of *trimethyl-2-quinolylammonium iodide*, m. p. 168° (Found, in material dried at 100°: C, 45·6; H, 4·6; N, 9·2. $C_{12}H_{15}N_2I$ requires C, 45·9; H, 4·8; N, 8·9%).

A solution of this compound (0·018 g.) in water (2 c.c.) was made alkaline (*ca.* pH 12) with sodium hydroxide and heated at 100° for 6 hr., then allowed to cool; fine needles separated. They were sublimed at 150°/0·2 mm. The sublimate (*ca.* 0·002 g.) had an infrared spectrum identical with that of 2-hydroxyquinoline.

*Reaction between 1-chloroisoquinoline and 4-methylmorpholine at 180°.* 1-Chloro*iso*quinoline (0·8 g.) was heated with excess of 4-methylmorpholine (4 c.c.) at 180° for 6 hr. 4 : 4-Dimethylmorpholinium chloride was isolated quantitatively as before (Found, in the purified product: C, 47·3; H, 9·0; N, 9·5%).

*Reaction between 1-chloroisoquinoline and trimethylamine at 30—35°.* A solution of 1-chloro-*iso*quinoline (1·3 g.) in excess of trimethylamine (*ca.* 10 g.) was kept in a sealed tube at 30—35° for 30 days, during which a small quantity of crystals separated. The excess of trimethylamine was then allowed to evaporate. The residue was washed with benzene, and the material remaining was dissolved in water (0·1 c.c.) and added to a saturated solution of potassium iodide (0·1 c.c.). The crystalline precipitate, obtained immediately, recrystallized from methanol as colourless prisms (*ca.* 0·003 g.). The infrared spectrum (in Nujol) of this substance was identical with that of tetramethylammonium iodide.

The author thanks Professor Sir Alexander Todd, F.R.S., and Dr. G. W. Kenner for their continued interest and advice, and the Department of Scientific and Industrial Research for the award of a maintenance allowance.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 26th*, 1957.]

## 175. *Some Anilinoquinones and N-Substituted 2-Hydroxy-1 : 4-naphthaquinone Imines.*

By M. Z. BARAKAT, S. K. SHEHAB, and M. M. EL-SADR.

WE believe that in its reaction [1,2] with *p*-benzoquinone in aqueous acetic acid one molecule of a primary aromatic amine adds at the ethylenic double bond of the quinone, and not at a C=O group, to form an additive product which is then oxidised by a second molecule of the quinone to produce the anilinoquinone. This explains why toluquinone yields only a monoanilide and *sym*-xyloquinone yields none [3,4] (steric hindrance).

By suitable selection of solvent and temperature, it is possible to make *p*-benzoquinone react with 1 or 2 mols. of a primary aromatic amine.[1] With various substituted anilines

[1] Suida and Suida, *Annalen*, 1918, **416**, 113.
[2] Martynoff and Tstsas, *Bull. Soc. chim. France*, 1947, 52.
[3] Shetsov and Shemyakin, *J. Gen. Chem.* (*U.S.S.R.*), 1949, **19**, 480.
[4] Cowdrey and Hinshelwood, *J.*, 1946, 1036.

we have obtained anilinoquinones in *ca.* 20% yield by reaction in very dilute aqueous acetic acid at <5°; these can be separated by means of light petroleum from the prevailing dianilinoquinones. At room temperature (25°) the product is entirely the dianilinoquinone.

Since naphthaquinone derivatives [5] have antibacterial properties,[5] including a curative effect on avian tuberculosis in white mice, we prepared some new *N*-substituted 2-hydroxy-1 : 4-naphthaquinone imines for evaluation as chemotherapeutic agents, using interaction of sodium 1 : 2-naphthaquinone-4-sulphonate with *p*-, *m*-, and *o*-chloroaniline and *o*-aminophenol.

*Experimental.*—All the anilinoquinones were insoluble in cold 10% alkali and gave purple colours in concentrated sulphuric acid. The tests for hydrogen peroxide and quinol in the filtrate of the reaction mixtures were positive in all cases.

*Reaction of* p-*benzoquinone with aniline.* (*a*) *p*-Benzoquinone (2·16 g.) was dissolved in hot distilled water (200 ml.), and the solution filtered from undissolved quinone, and cooled in ice. Freshly distilled aniline (0·93 g., 0·01 mol.) was suspended in distilled water (75 ml.), and glacial acetic acid was stirred in until dissolution was complete. This solution was added in portions (about 5 ml.) to the cold quinone solution with continuous shaking. Maroon-coloured crystals began to be deposited. The mixture was kept in ice for 15 min. and filtered. The solid monoanilino-quinone, recrystallised from light petroleum (b. p. 60—80°), had m. p. 139° (decomp.) (lit., m. p. 119°) (Found: C, 72·4; H, 4·45; N, 7·15. Calc. for $C_{12}H_9O_2N$: C, 72·4; H, 4·5; N, 7·0%) (yield, 0·4 g.). In concentrated sulphuric acid, it gave a purple-violet colour. The filtrate gave a positive test for peroxide with potassium iodide–starch and acetic acid, and on evaporation and recrystallisation of the residue from water gave quinol (mixed m. p.).

(*b*) The same reactants, but 2 mols. of aniline, when shaken at 25°, at once deposited red-violet crystals. After 30 minutes' shaking, filtration gave the dianilinoquinone which, recrystallised from nitrobenzene, had m. p. 224° (decomp.) (Found: C, 74·4; H, 4·8; N, 9·65. Calc. for $C_{18}H_{14}O_2N_2$: C, 74·5; H, 4·8; N, 9·7%) (yield 1·48 g.).

The following were similarly prepared and crystallised: 2-o-*chloro*-, brick red, m. p. 110—111° (decomp.) (Found: C, 62·2; H, 3·5; N, 6·5; Cl, 15·6. $C_{12}H_8O_2NCl$ requires C, 61·7; H, 3·4; N, 6·0; Cl, 15·2%), and 2-m-*chloro-anilino*-1 : 4-*benzoquinone*, violet-black, m. p. 106° (decomp.) (Found: C, 62·0; H, 3·7; N, 5·8; Cl, 15·9%); 2 : 5-*di*-o-*chloro*-, brick-red (cryst. from alcohol), m. p. 220—222° (decomp.) (Found: C, 60·4; H, 3·6; N, 7·4; Cl, 19·6. $C_{18}H_{12}O_2N_2Cl_2$ requires C, 60·2; H, 3·3; N, 7·8; Cl, 19·8%), 2 : 5-*di*-m-*chloro*-, maroon, m. p. 270—272° (decomp.) (Found: C, 59·8; H, 3·2; N, 8·25; Cl, 19·9%), and 2 : 5-*di*-p-*bromo-anilino*-1 : 4-*benzoquinone*, violet-black, m. p. >300° (Found: C, 48·7; H, 2·9; N, 7·0; Br, 34·4. $C_{18}H_{12}O_2N_2Br_2$ requires C, 48·2; H, 2·7; N, 6·25; Br, 35·7%).

*Naphthaquinones.* The products were free from sulphur and dissolved in 10% alkali.

Solutions of *p*-chloroaniline (1·275 g.) in ethanol (40 ml.) and of sodium 1 : 2-naphthaquinone-4-sulphonate (5·20 g.) in water (200 ml.), when mixed and kept for 10 min., deposited 2-*hydroxy*-1 : 4-*naphthaquinone* p-*chlorophenylimine*, red-brown (from acetone), m. p. 280—282° (decomp.) (Found: C, 68·1; H, 3·2; N, 4·9; Cl, 12·7; active H, 0·43. $C_{16}H_{10}O_2NCl$ requires C, 67·7; H, 3·5; N, 4·9; Cl, 12·5; 1H, 0·35%) (yield 2·60 g.).

Similar reactions gave the m-*chlorophenylimine*, brownish-red, m. p. 292—294° (Found: C, 67·7; H, 3·4; N, 4·3; Cl, 12·55%), o-*chlorophenylimine*, brick-red, m. p. 266° (decomp.) (Found: C, 67·6; H, 3·7; N, 5·0; Cl, 12·6%), and o-*hydroxyphenylimine*, brick-red, m. p. 246—248° (decomp.) (Found: C, 72·7; H, 4·3; N, 5·55. $C_{16}H_{11}O_3N$ requires C, 72·45; H, 4·15; N, 5·3%) (positive test with phosphotungstic acid indicating more than one phenolic group).

BIOCHEMISTRY DEPARTMENT, FACULTY OF VETERINARY MEDICINE,
CAIRO UNIVERSITY, GIZA, CAIRO, EGYPT.

[*Received, May 27th*, 1957.]

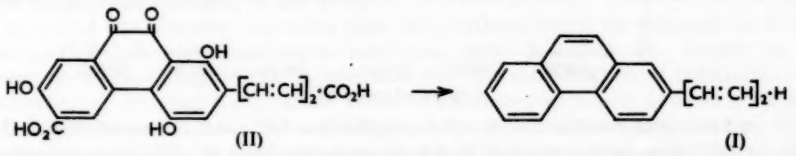
[5] Rubstov, *J. Gen. Chem.* (*U.S.S.R.*), 1946, **16**, 221.

## 176. *Researches on Polyenes. Part VI.* The Synthesis of* trans-1-2′-*Phenanthrylbuta*-1 : 3-*diene.*

By B. B. Millward and M. C. Whiting.

During degradations of the fungus pigment telephoric acid, Kögl, Erxleben, and Jänecki [1] isolated a hydrocarbon, $C_{18}H_{14}$, formed in good yield (~15%) by zinc-dust distillation of the triacetate. It gave 2-phenanthroic acid on oxidation. Since hexahydrotelephoric acid gave adipic acid on oxidation, the $C_{18}H_{14}$ hydrocarbon was formulated as 1-2′-phenanthrylbuta-1 : 3-diene (I) rather than the 2-compound. These results were part of the evidence on which structure (II) was advanced for telephoric acid.

The preparation of a series of 1-arylbut-2-en-1-ols,[2] including the 2-naphthyl and 9-phenanthryl derivatives, and the dehydration of several substituted 1-phenylbut-2-en-1-ols to the corresponding phenylbutadienes [3] suggested a straightforward synthesis of 1-2′-phenanthrylbuta-1 : 3-diene (I). Indeed, 2-bromophenanthrene [4] was converted into the corresponding arylbutenol by the interaction of its Grignard reagent, prepared in the presence of an equimolecular amount of ethylmagnesium bromide, with crotonaldehyde,[2] although careful purification of the bromide proved necessary. Dehydration




(II) (I)

as described by Braude, Jones, and Stern [3] was unsatisfactory, however, for both the phenanthrylbutenol and the 2-naphthyl analogue. It is noteworthy that despite the ease with which 1-phenylethanol is dehydrated, Price and Halpern [5] were unable to obtain the 2-, 3-, or 9-vinylphenanthrene by treating the corresponding 1-arylethanols with potassium hydrogen sulphate or thionyl chloride and pyridine. After several methods had been unsuccessful—although all gave spectroscopically detectable amounts of the required diene along with much polymer—toluene-*p*-sulphonic acid in benzene at 80° proved satisfactory. Optimal reaction times, roughly determined spectroscopically, were about 15 minutes and 1 minute for the 2′-naphthyl- and 2′-phenanthrylbutenols. The two dienes were rather unstable solids, m. p. 92—94° and 107—109°, respectively.

During the dehydration work, 1-2′-phenanthrylbut-2-en-1-ol was rearranged in good yield to the corresponding 4-arylbut-3-en-2-ol by sulphuric acid in aqueous dioxan. The rate constant was of the same order as that reported for other arylbutenols.[3]

The infrared spectra of the new dienes were similar, and, in particular, each showed bands at 892 and 1000 cm.$^{-1}$, attributable to a vinyl group, and at 945 cm.$^{-1}$, attributable to a *trans*-1 : 2-disubstituted ethylenic linkage. The best proof of structure, however, is the ultraviolet absorption spectra (Figs. 1 and 2), which can be compared with those of the corresponding phenyl compounds,[2] the analogy then becoming convincing.

Kögl, Erxleben, and Jänecki report only the melting point (125°) for their hydrocarbon; and Professor Kögl has informed us [6] that no sample has survived. In view of the difficulty of isolating telephoric acid, the situation remains unsatisfactory. It seems unlikely, though possible, that our diene was a low-melting polymorph. The naturally-derived hydrocarbon might be the *cis*-isomer, if that were (*a*) stable under pyrolytic conditions and (*b*)

* Part V, *J.*, 1957, 537.

[1] Kögl, Erxleben, and Jänecki, *Annalen*, 1930, **482**, 105.
[2] Braude, Jones, and Stern, *J.*, 1947, 1087.
[3] Braude, Fawcett, and Newman, *J.*, 1950, 793.
[4] Mossettig and de Kamp, *J. Amer. Chem. Soc.*, 1930, **52**, 3704; Bachmann and Boatner, *ibid.*, 1936, **58**, 2097, 2194; Dice and Smith, *J. Org. Chem.*, 1949, **14**, 179.
[5] Price and Halpern, *J. Amer. Chem. Soc.*, 1951, **73**, 818.
[6] Personal communication from Prof. F. Kögl.

XUM

higher melting than the *trans*-form. Finally, the hydrocarbon, m. p. 125°, may not have been 1-2′-phenanthrylbuta-1 : 3-diene; but in that case we can neither suggest an alternative formula for it based on structure (II) for telephoric acid, nor propose another structure for telephoric acid consistent with the published evidence.

FIG. 1. FIG. 2.

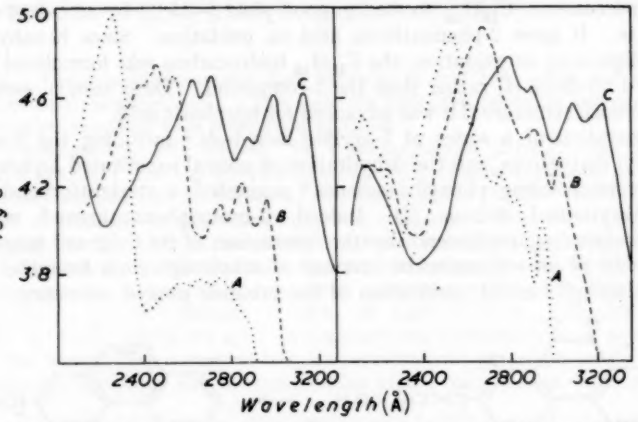



FIG. 1. *A*, 1-2′-*Naphthylbut*-2-*en*-1-*ol*; *B*, 4-2′-*naphthylbut*-3-*en*-2-*ol*; *and C*, 1-2′-*naphthylbuta*-1 : 3-*diene*.

FIG. 2. *A*, 1-2′-*Phenanthrylbut*-2-*en*-1-*ol*; *B*, 4-2′-*phenanthrylbut*-3-*en*-2-*ol*; *and C*, 1-2′-*phenanthrylbuta*-1 : 3-*diene*.

*Experimental.*—" Alumina " refers to Peter Spence, Grade H. Ultraviolet and infrared spectra were determined in ethanol and carbon disulphide, respectively. M. p.s were determined on a Kofler block.

trans-1-2′-*Naphthylbuta*-1 : 3-*diene*. (*a*) *trans*-1-2′-Naphthylbut-2-en-1-ol [3] (50 mg.), toluene-*p*-sulphonic acid (5 mg.), and benzene (25 c.c.) were heated under reflux, the reaction being followed spectroscopically. After 30 min.—beyond the point of optimal yield—the mixture was cooled, washed with sodium hydrogen carbonate solution, and evaporated under reduced pressure. The residue was extracted with methanol; addition of water gave the *diene* (18 mg., 45%) as plates, m. p. 91—94° (Found: C, 93·0; H, 6·8. $C_{14}H_{12}$ requires C, 93·3; H, 6·7%).

(*b*) *trans*-4-2′-Naphthylbut-3-en-2-ol [3] (133 mg.) was similarly dehydrated with toluene-*p*-sulphonic acid (14 mg.) in boiling benzene (50 c.c.), with the exclusion of light. Isolation of the product gave a solid, m. p. 87—94° (114 mg., 94%) which after chromatographic purification and crystallisation had m. p. 92—94°.

trans-1-2′-*Phenanthrylbut*-2-*en*-1-*ol*. A mixture of 2-bromophenanthrene [4] (3·0 g.), ethyl bromide (0·9 c.c.), benzene (15 c.c.), ether (30 c.c.), and magnesium (0·7 g.) was heated under reflux for 7 hr., then cooled to 0° whilst crotonaldehyde (2·0 g.) in ether (20 c.c.) and benzene (20 c.c.) was added dropwise. After 15 min. saturated ammonium chloride solution was added, and the aqueous solution extracted with benzene. Evaporation under reduced pressure gave a residue which, in light petroleum–benzene (3 : 2), was chromatographed on alumina. Elution with benzene containing 2% of methanol gave a residue which was extracted with pentane; evaporation and crystallisation (from aqueous ethanol) gave the *alcohol* as needles, m. p. 92—95° (Found: C, 86·9; H, 6·5. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%).

trans-4-2′-*Phenanthrylbut*-3-*en*-2-*ol*. The above alcohol (174 mg.) was dissolved in 0·01M-sulphuric acid in 60% dioxan. After 20 hr. addition of water and crystallisation from benzene–light petroleum gave the rearranged *alcohol* (130 mg., 75%) as prisms, m. p. 137—139° (Found: C, 86·8; H, 6·5%).

trans-1-2′-*Phenanthrylbuta*-1 : 3-*diene*. To toluene-*p*-sulphonic acid (21 mg.) in boiling benzene (50 c.c.), 1-2′-phenanthrylbut-2-en-1-ol (206 mg.) was added. After 1 min. the mixture was rapidly chilled and the solution was washed with sodium hydrogen carbonate solution. After evaporation under reduced pressure at 20° the residue, in benzene–light petroleum (1 : 20),

was chromatographed on alumina. Evaporation at 20° and crystallisation from methanol gave the required diene (62 mg., 32%), m. p. 107—109° (Found: C, 93·9; H, 6·0. $C_{18}H_{14}$ requires C, 93·9; H, 6·1%). The diene polymerised during 2 months at −30° in the absence of bright light. Irradiation with ultraviolet light rapidly reduced the intensity of the absorption maxima at 3230 and 3090 Å.

Analyses and spectrographic measurements were by Mr. E. S. Morton and Mr. H. Smith, and by Miss W. Peadon and Mrs. J. Hopkins, respectively.

THE UNIVERSITY, MANCHESTER.
THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, September 4th*, 1957.]

[7] Cf. Grummitt and Christolph, *J. Amer. Chem. Soc.*, 1951, **73**, 3479.

---

## 177. *A Synthesis of* 3-O-β-D-*Galactopyranosyl*-D-*galactose.*

By D. H. BALL and J. K. N. JONES.

THE isolation of the 1 : 6- and 1 : 3-β-linked isomers of *O*-D-galactopyranosyl-D-galactose from gums,[1] wood polysaccharides,[2] and galactogen [3] has recently been described. The former isomer was prepared several years ago by Freudenberg and his co-workers [4] and we now describe the synthesis of the latter.

A survey of the literature indicated that this synthesis might be achieved *via* 4 : 6-*O*-ethylidene-1 : 2-*O*-*iso*propylidene-D-galactose (*A*), first described by Foster *et al.*[5] However, in the first stage of this preparation, *viz.*, the condensation of D-galactose with paraldehyde, we obtained a crystalline 4 : 6-*O*-ethylidene-D-galactose and not a syrup as described by these workers. The crystalline compound condensed with acetone in the presence of zinc chloride to form a syrupy *iso*propylidene derivative, which was purified *via* its crystalline toluene-*p*-sulphonate. This ester had a high positive specific rotation (+119°) and was converted into the desired derivative by reduction with lithium aluminium hydride. Methylation with silver oxide and methyl iodide then gave a syrupy *O*-methyl derivative which on hydrolysis yielded a crystalline 3-*O*-methyl-D-galactose, proving that the compound (*A*) has a free hydroxyl group at position 3.

The compound previously thought to be the 3-*O*-toluene-*p*-sulphonate of compound (*A*) had a negative specific rotation [5] (−67°) and is believed to be 3 : 4-*O*-ethylidene-1 : 2-*O*-*iso*propylidene-D-galactose 6-*O*-toluene-*p*-sulphonate. This compound was isolated on acylation of the substance formed when 4 : 6-*O*-ethylidene-D-galactose is condensed with acetone in the presence of phosphoric oxide (details of this work will be given later).

Condensation of acetobromo-D-galactose with compound (*A*) by the method of Haskins *et al.*[7] gave a syrup which was heated with an excess of sodium hydroxide solution to saponify acetyl groups and to destroy reducing sugars. The mixture was then deionised and heated with acetic acid in order to hydrolyse *O*-ethylidene and *O*-*iso*propylidene groups. The mixture of sugars was fractionated on a cellulose column, and crystalline 3-*O*-β-D-galactopyranosyl-D-galactose was obtained.

*Experimental.*—Paper chromatography was carried out by the descending method [8] on Whatman No. 1 filter paper, the following solvent systems being used: (*a*) butan-1-ol–ethanol–water (3 : 1 : 1); (*b*) butan-1-ol–pyridine–water (10 : 3 : 3); (*c*) ethyl acetate–acetic acid–water (9 : 2 : 2); and (*d*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4) (all v/v). The positions of the sugars on the chromatograms were determined by spraying either with silver nitrate in acetone followed by sodium hydroxide [9] in ethanol or with *p*-anisidine hydrochloride

[1] Jackson and Smith, *J.*, 1940, 79; Hirst and Perlin, *J.*, 1954, 2622.
[2] White, *J. Amer. Chem. Soc.*, 1942, **64**, 302; Bouveng and Lindberg, *Acta Chem. Scand.*, 1956, **10**, 1515.
[3] Weinland, *Z. physiol. Chem.*, 1956, **305**, 87.
[4] Freudenberg, Wolf, Knopf, and Zaheer, *Ber.*, 1928, **61**, 1743.
[5] Foster, Overend, and Stacey, *J.*, 1951, 980.
[6] Cf. Bouveng and Lindberg, *Acta Chem. Scand.*, 1956, **10**, 1283.
[7] Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1724.
[8] Partridge, *Biochem. J.*, 1948, **42**, 238.
[9] Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444.

XUM

in butan-1-ol.[10] The rates of movement of the sugars are quoted relative to that of galactose ($R_{gal}$) on the same chromatogram. Optical rotations were determined at 23° ± 3° (unless otherwise stated, solution was in water and the figures given are equilibrium values). Solvents were removed under reduced pressure.

4 : 6-O-*Ethylidene*-D-*galactose*. To a suspension of finely powdered D-galactose (60 g.) in redistilled paraldehyde (220 ml.) was added concentrated sulphuric acid (0·6 ml.), and the mixture was shaken at room temperature for 24 hr. The solid was collected, washed with cold ethanol, and extracted with boiling ethanol which contained sufficient ammonia to neutralise residual acid. The hot solution was filtered to remove galactose and allowed to cool. The product (40 g., 58%) moved at the rate of rhamnose (solvent *a*) and contained traces of galactose. After two recrystallisations from ethanol, it had m. p. 185° and $[\alpha]_D$ +122° (20 min.) ⟶ +96° (4 hr., constant) (*c* 2·0). The *compound* therefore crystallises in the α-form (Found: C, 46·8; H, 6·8. $C_8H_{14}O_6$ requires C, 46·6; H, 6·8%). If the condensation is carried out in the presence of greater amounts of sulphuric acid as catalyst, a syrupy mixture of ethylidene derivatives results. Toluene-*p*-sulphonylation of this material gave, in one case, a crystalline compound thought to be 1 : 2-3 : 4-*di*-O-*ethylidene*-D-*galactose* 6-O-*toluene*-p-*sulphonate*. It had m. p. 119—122° and $[\alpha]_D$ −68° (*c* 1·0 in $CHCl_3$) (Found: C, 53·0; H, 5·7; S, 8·0. $C_{17}H_{22}O_8S$ requires C, 52·8; H, 5·7; S, 8·3%).

4 : 6-O-*Ethylidene*-D-*galactose* p-*nitrophenylhydrazone* was prepared by heating 4 : 6-*O*-ethylidene-D-galactose for 1 hr. with alcoholic *p*-nitrophenylhydrazine. It had m. p. 248° (decomp.) (Found: C, 49·1; H, 5·5; N, 12·5. $C_{14}H_{19}O_7N_3$ requires C, 49·2; H, 5·6; N, 12·6%).

*Condensation of* 4 : 6-O-*ethylidene*-D-*galactose with acetone*. The ethylidene compound (20 g.) was ground and suspended in acetone (500 ml.). Granular zinc chloride (50 g.) was added and the mixture was shaken. After 70 hr., a further portion (10 g.) of zinc chloride was added. After a further 45 hr., the mixture was homogeneous and the colourless solution was poured into a stirred solution of sodium carbonate (70 g.) in water (2 l.). The precipitated zinc salts were removed and extracted twice with boiling acetone. The combined filtrate and extracts were concentrated to remove acetone, and the residual aqueous solution (*ca.* 400 ml.) was then extracted with chloroform (5 × 50 ml.). The extracts were dried ($Na_2SO_4$) and concentrated to a syrup (8·9 g.). The condensation product gave one spot on paper chromatograms at $R_F$ 0·8 (solvent *a*). It gave a yellow colour with the *p*-anisidine spray.

The syrupy condensation product (8·9 g.) was treated with toluene-*p*-sulphonyl chloride (7·6 g., 1·1 equiv.) in dry pyridine (40 ml.). The solution was left overnight at 20°, then heated at 80° for 20 min., cooled, and poured into ice-water (1 l.). The product separated as a gum which rapidly solidified. The crude light brown powder (12·5 g.) crystallised from hot ethanol and after further recrystallisation from methanol 4 : 6-O-*ethylidene*-1 : 2-O-iso*propylidene*-D-*galactose* 3-*toluene*-p-*sulphonate* had m. p. 116—118°, $[\alpha]_D$ +119° (*c* 1·0 in $CHCl_3$) (Found: C, 54·1; H, 6·0; S, 7·8. $C_{18}H_{24}O_8S$ requires C, 54·0; H, 6·0; S, 8·0%).

3-O-*Methyl*-D-*galactose*. The preceding ester (3·0 g.) was dissolved in a mixture of sodium-dried benzene (4 ml.) and sodium-dried ether (8 ml.). The solution was boiled under reflux and powdered lithium aluminium hydride (0·60 g.) was added in three portions during 36 hr. After 60 hr., the mixture was cooled and poured on ice, and the 4 : 6-*O*-ethylidene-1 : 2-*O*-isopropylidene-D-galactose (1·7 g.) was isolated by chloroform extraction of the aqueous solution. A portion of the syrup (0·40 g.) was methylated with sodium hydroxide and methyl sulphate in the usual way; the product (0·35 g.), purified by distillation, had b. p. 110—120° (bath temp.)/0·04 mm., $n_D^{20}$ 1·4640. The syrup was heated in N-sulphuric acid at 100° for 1 hr. The solution was neutralised (Amberlite mixed-bed resin MB-3) and concentrated to a syrup which crystallised readily when nucleated with an authentic specimen of 3-*O*-methyl-D-galactose. The product, recrystallised from ethanol–acetone, had m. p. and mixed m. p. 139—143°. It was indistinguishable from 3-*O*-methylgalactose on paper chromatograms (solvents *a*, *b*, *c*, and *d*) and on paper electrophoretograms.[6]

*Synthesis of* 3-O-β-D-*galactopyranosyl*-D-*galactose*. 4 : 6-*O*-Ethylidene-1 : 2-*O*-isopropylidene-D-galactose (from the 3-*O*-toluene-*p*-sulphonate) (1·7 g., 0·007 mole) was dissolved in dry, alcohol-free chloroform (15 ml.) and to the solution was added Drierite (10 g.), silver oxide (5 g.), and glass beads. The mixture was shaken in the dark. After 1 hr., acetobromo-D-galactose (2·88 g., 0·007 mole) in dry, alcohol-free chloroform (10 ml.) and iodine (0·5 g.) were added and the shaking was continued. After 4 days, a test for ionisable bromine was negative and the above additions were repeated. The mixture was shaken for a further 4 days and then

[10] Hough, Jones, and Wadman, *J.*, 1950, 1702.

filtered and to the cooled filtrate was added a solution of sodium methoxide in methanol (10 ml.). A precipitate of galactose was removed and the filtrate concentrated to a syrup. This was taken up in water and extracted continuously with chloroform to remove unchanged acetals of galactose. The aqueous solution was then deionised and concentrated to a syrup (1·5 g.) which was fractionated on filter paper (Whatman No. 3MM). The main fraction was non-reducing and moved slightly faster than rhamnose. This material was isolated from the paper, and the acetal groups were removed by boiling it with dilute acetic acid for 3 hr. Concentration of the acidic solution gave a syrup which contained galactose and a disaccharide. These were separated on filter paper (Whatman No. 3MM), and the disaccharide fraction (0·16 g.) crystallised when nucleated with authentic 3-*O*-β-D-galactopyranosyl-D-galactose. After recrystallisation from aqueous methanol containing a little butan-1-ol, the crystals had m. p. 163—170° undepressed by admixture with an authentic specimen, and $[\alpha]_D$ +75° (5 min.) ⟶ +60° (2 hr., const.) (*c* 2·0). The synthetic disaccharide was indistinguishable on paper chromatograms from authentic material, and infrared analysis indicated that the synthetic and authentic materials were identical.

We thank the National Research Council of Canada for a grant and one of us (D. H. B.) acknowledges the award of a scholarship.

QUEEN'S UNIVERSITY, KINGSTON, ONTARIO, CANADA. [*Received, September 6th,* 1957.]

---

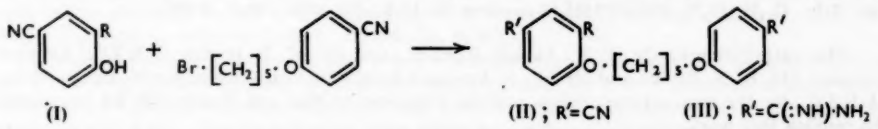
## 178. *Search for Chemotherapeutic Amidines. Part XV.* 2-Methoxy- and 2-Hydroxy-derivatives of* 1 : 5-*Di*-p-*amidinophenoxypentane.*

By M. DAVIS.

THE trypanocidal activity of 4 : 4′-diamidinostilbene ("Stilbamidine") is retained on introduction of a 2-methoxy-group into one ring, and is increased on the introduction of a 2-hydroxy-group.[1] Some mono- and di-substituted αω-di-*p*-amidinophenoxyalkanes have also been prepared,[2] but none of these contained a single 2-methoxy- or 2-hydroxy-group. Corresponding monosubstituted derivatives of "Pentamidine" (III; R = H) are now described.

Condensation of 4-cyano-2-methoxyphenol[3] (I; R = OMe) with 5-*p*-cyanophenoxypentyl bromide[2] gave the dinitrile (II; R = OMe) in high yield, which was converted into the diamidine (III; R = OMe) in the usual way.[4]

It is known that 4-nitrocatechol can be preferentially alkylated in the 1-position[5] and it seemed likely that 4-cyanocatechol[6] could be similarly converted into a 1-monoether. In the event, condensation of 4-cyanocatechol (I; R = OH) with 5-*p*-cyanophenoxypentyl




(I) (II); R′=CN (III); R′=C(:NH)·NH$_2$

bromide gave a mixture of the required dinitrile (II; R = OH) and the trinitrile (II; R = O·[CH$_2$]$_5$·O·C$_6$H$_4$·CN-*p*). The phenolic component was readily isolated as the crystalline sodium salt; its orientation was confirmed by methylation to the dinitrile (II; R = OMe). Its conversion into the diamidine (III; R = OH) proceeded normally.

Biological tests showed that the two diamidines possessed trypanocidal and antibacterial properties similar to those of "Pentamidine". Thus, the $LD_{50}$ (mg./g., subcutaneously in mice) for the diamidines (III; R = OMe) and (III; R = OH) were

* Part XIV, *J.*, 1957, 3089.

[1] Ashley and Harris, *J.*, 1946, 567.
[2] Berg and Newbery, *J.*, 1949, 642.
[3] Marcus, *Ber.*, 1891, **24**, 3654.
[4] Ashley and MacDonald, *J.*, 1957, 1668.
[5] Cardwell and Robinson, *J.*, 1915, 255.
[6] Ewins, *J.*, 1909, 1482.

respectively 0·175 and 0·075 (" Pentamidine ", 0·166). The corresponding $CD_{50}$ against *T. rhodesiense* were respectively 0·0025 and 0·003 (" Pentamidine ", 0·002). Neither compound was curative against *T. congolense* in mice.

*Experimental.*—1-(4-*Cyano*-2-*methoxyphenoxy*)-5-p-*cyanophenoxypentane*. 4-Cyano-2-methoxyphenol (29·8 g.) and 5-*p*-cyanophenoxypentyl bromide (53·6 g.) were added successively to sodium hydroxide (8 g.) in water (10 ml.) and 2-ethoxyethanol (100 ml.). The mixture was refluxed for 20 hr., cooled, and diluted with water. The *dinitrile* (55·25 g., 82%) had m. p. 115—117° after recrystallisations from ethanol (Found: N, 8·4. $C_{20}H_{20}O_3N_2$ requires N, 8·3%).

1-(4-*Cyano*-2-*hydroxyphenoxy*)-5-p-*cyanophenoxypentane*. Potassium hydroxide (6·1 g.) in water (10 ml.) and 2-ethoxyethanol (10 ml.) was added during 1·5 hr. to a refluxing solution of 4-cyanocatechol (14·75 g.) and 5-*p*-cyanophenoxypentyl bromide (29·3 g.) in 2-ethoxyethanol (50 ml.). After another 3·5 hr. the mixture was cooled, shaken with chloroform and dilute hydrochloric acid, and filtered. The *dinitrile* (4·8 g.) had m. p. 141—143° after recrystallisations from ethanol and from toluene (Found: C, 70·7; H, 5·9; N, 8·8. $C_{19}H_{18}O_3N_2$ requires C, 70·8; H, 5·6; N, 8·7%). More (7·7 g., m. p. 140—142°) of the product was obtained by treatment of the chloroform solution with dilute sodium hydroxide solution, separation of the crystalline sodium salt, and acidification. Its structure was confirmed by methylation with methyl iodide and potassium carbonate in acetone. The 2-methoxy-compound had m. p. 114—115° and mixed m. p. 114·5—115·5° with authentic material. The chloroform solution, after removal of the sodium salt, was washed, dried, and evaporated. The residue, in benzene, was filtered through alumina and the eluate on evaporation yielded 1-[4-*cyano*-2-(5-p-*cyanophenoxypentyloxy*)-*phenoxy*]-5-p-*cyanophenoxypentane* (7·4 g.), m. p. 81—83° [from acetone–light petroleum (b. p. 40—60°)] (Found: C, 72·9; H, 6·2; N, 8·1. $C_{31}H_{31}O_4N_3$ requires C, 73·1; H, 6·1; N, 8·2%).

1-(4-*Amidino*-2-*methoxyphenoxy*)-5-p-*amidinophenoxypentane*. The dinitrile (30 g.) in dry chloroform (200 ml.) and ethanol (30 ml.) was treated with hydrogen chloride for 1 hr. at 0°. After 10 days at room temperature, the suspension was diluted with dry ether and the di-imidoate dihydrochloride was filtered off and dried. It was then added to saturated ethanolic ammonia (400 ml.) at 0° and the mixture was kept for 1·5 hr. at 0° and for 3 hr. at 60—70°, and filtered. The filtrate on cooling deposited the diamidine dihydrochloride (9·35 g.), which melts and effervesces above 165°. A second crop (19·7 g.) was obtained by concentrating the mother liquors *in vacuo*. The combined products yielded 1-(4-*amidino*-2-*methoxyphenoxy*)-5-p-*amidinophenoxypentane dihydrochloride sesquihydrate* (19·85 g.) (from ethanol), which slowly melted and effervesced above 155° (Found: C, 51·9; H, 6·6; N, 11·9; Cl, 15·1, loss at 110°/15 mm., 5·6. $C_{20}H_{26}O_2N_4,2HCl,1{\cdot}5H_2O$ requires C, 51·1; H, 6·6; N, 11·9; Cl, 15·1; $H_2O$, 5·7%).

1-(4-*Amidino*-2-*hydroxyphenoxy*)-5-p-*amidinophenoxypentane dihydrochloride*, similarly prepared, was purified by dissolution in very dilute hydrochloric acid and addition of concentrated hydrochloric acid. It separated as a *hydrate*, which slowly melted and effervesced above 201° (Found: N, 12·2; Cl, 15·55; loss at 100°/15 mm, 6·6; regain in air, 7·1. $C_{19}H_{24}O_3N_4,2HCl,1{\cdot}75H_2O$ requires N, 12·1; Cl, 15·4; $H_2O$, 6·8%).

The author thanks Dr. J. N. Ashley, F.R.I.C., and Dr. H. J. Barber, F.R.I.C., for their interest, Mr. K. N. Brown and Mr. W. A. Freeman for the biological tests, Mr. S. Bance, B.Sc., A.R.I.C., for the semi-microanalyses, and the Directors of May and Baker Ltd. for permission to publish this work.

RESEARCH LABORATORIES,
MAY AND BAKER, LTD., DAGENHAM, ESSEX. [*Received, September 9th*, 1957.]

---

## 179. *Certain Reactions of 4-Methoxydiphenyl.*

By W. H. LINNELL and H. J. SMITH.

A POSSIBLE synthesis of certain analogues of steroidal hormones [1] required 4'-methoxy-4-diphenylylacetic acid. Although this acid was finally prepared in good yield from 4'-methoxy-4-diphenylyl methyl ketone by a Kindler variation of the Willgerodt reaction initially the chloromethylation of 4-methoxydiphenyl was studied. Kosolapoff's method [2] yielded a solid containing 55% of chloromethyl compound which on reaction with cyanide

[1] Linnell and Smith, in the press.
[2] Kosolapoff, *J. Amer. Chem. Soc.*, 1946, **68**, 1670.

followed by alkaline hydrolysis gave an acid (m. p. 169—169·5°), isomeric with the required acetic acid (m. p. 188—188·5° [1]). Fieser and Bradsher [3] has described the Friedel–Crafts acylation of 4-methoxydiphenyl, substitution mainly occurring in the 4′-position, whereas nitration gives 4-methoxy-3-nitrodiphenyl.[4] Our acid, m. p. 169—169·5°, was therefore tentatively formulated as 4-methoxy-3-diphenylylacetic acid, this formulation being confirmed by independent synthesis.

A Gattermann reaction with 4-methoxydiphenyl yielded an aldehyde, oxidised to the known 4-methoxydiphenyl-3-carboxylic acid [5] by permanganate. This acid was converted by the Arndt–Eistert method into 4-methoxy-3-diphenylylacetic acid, identical with the acid prepared by chloromethylation of 4-methoxydiphenyl.

*Experimental.—Chloromethylation of 4-methoxydiphenyl.* 4-Methoxydiphenyl (17·85 g.), paraformaldehyde (2 g.), acetic acid (25 c.c.), hydrochloric acid (*d* 1·18; 28 c.c.), phosphoric acid (85%, 13·5 c.c.), and light petroleum (b. p. 60—80°, 50 c.c.) were refluxed with stirring for 20 hr. and then cooled and extracted with chloroform. The extract was washed free from acid, dried ($Na_2SO_4$), and evaporated to a solid (17·1 g.), m. p. 78·5—83°. The chloromethyl compound could not be isolated from this mixture by distillation or crystallisation. The solid was estimated to contain 55% of chloromethyl compound (monochloromethylation being assumed) by hydrolysis with alcoholic alkali and determination of the chloride ion by Volhard's method.

*Reaction of chloromethyl compound with cyanide.* Crude chloromethylated material (8·3 g.) in alcohol (70 c.c.) and sodium cyanide (6 g.) in water (8 c.c.) were refluxed for 13 hr.; aqueous potassium hydroxide was then added and refluxing was continued for 22 hr. The solution was then worked up to give *4-methoxy-3-diphenylylacetic acid* (4·35 g.), m. p. and mixed m. p. 169—169·5° (from aqueous alcohol) (Found: C, 74·1; H, 5·8%; equiv., 241. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%; equiv., 242·3). The amide was obtained as long white needles (from aqueous alcohol), m. p. and mixed m. p. 181·5—181·8°, and the *p*-bromophenacyl ester as white microneedles (from alcohol), m. p. 131·5° undepressed on admixture with authentic material (Found: C, 62·8; H, 4·45; Br, 17·9. Calc. for $C_{24}H_{21}O_4Br$: C, 62·9; H, 4·4; Br, 18·2%).

*4-Methoxydiphenyl-3-aldehyde.* Zinc cyanide (46·8 g.) and potassium chloride (5 g.) were added to 4-methoxydiphenyl (36·8 g.) in dry benzene (220 c.c.) and a rapid stream of dry hydrogen chloride passed in with stirring for 2½ hr. Aluminium chloride (40 g.) was then added and gas passed through the mixture at 40—50° for a further 4 hr. The benzene layer was separated, hydrochloric acid added, and the mixture refluxed for 1 hr. The upper layer which separated upon cooling was dried and the aldehydic fraction was isolated from this by decomposition of its semicarbazone (indicated 48% of aldehydic material present) with dilute sulphuric acid. Recrystallisation gave an *aldehyde*, m. p. 76·5—77° (Found: C, 79·45; H, 5·6; MeO, 14·2. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7; MeO, 14·6%). The orange-red 2 : 4-*dinitrophenylhydrazone* had m. p. 230—231·5° (from aqueous acetic acid) (Found: C, 61·6; H, 4·2; N, 14·2. $C_{20}H_{16}O_5N_4$ requires C, 61·2; H, 4·1; N, 14·3%). The *semicarbazone* was obtained as pale yellow plates, m. p. 239·5—240° (from aqueous acetic acid) (Found: C, 66·8; H, 5·55; N, 15·9. $C_{15}H_{15}O_2N_3$ requires C, 66·9; H, 5·6; N, 15·6%).

*4-Methoxydiphenyl-3-carboxylic acid.* 4-Methoxydiphenyl-3-aldehyde (2·6 g.) was oxidised by a refluxing alkaline solution of potassium permanganate for 3 hr. Removal of manganese dioxide and addition of hydrochloric acid and a little sodium hydrogen sulphite gave a white precipitate (2·1 g.). Recrystallisation from ether gave pale yellow micro-crystals of the acid, m. p. 170—170·5° (lit.[3] gives m. p. 166—167°) (Found: C, 74·4; H, 5·4; MeO, 13·4%; equiv., 233·7. Calc. for $C_{14}H_{12}O_3$: C, 73·7; H, 5·3; MeO, 13·6%; equiv., 228·2).

*4-Hydroxydiphenyl-3-carboxylic acid.* 4-Methoxydiphenyl-3-carboxylic acid was quantitatively demethylated by acetic acid and 48% hydrogen bromide solution, to give white microcrystals of the hydroxy-acid, m. p. 214—214·5° (lit. gives m. p. 212—213°) (from *cyclo*hexane) (Found: C, 73·0; H, 4·8. Calc. for $C_{13}H_{10}O_3$: C, 72·9; H, 4·7%). The methyl ester was obtained as white micro-needles, m. p. 93—94° (lit.[3] gives m. p. 93—94°) (Found: C, 74·0; H, 5·1. Calc. for $C_{14}H_{12}O_3$: C, 73·7; H, 5·3%).

*4-Methoxy-3-diphenylylacetic acid.* 4-Methoxydiphenyl-3-carboxylic acid (3·2 g.) and freshly distilled thionyl chloride (25 c.c.) were refluxed for 1 hr. and excess of thionyl chloride then removed. The acid chloride in dioxan (20 c.c.) was added to ice-cold ethereal diazomethane (600 c.c.; prepared from 15 g. of methylnitrosourea), and left overnight. Removal

[3] Fieser and Bradsher, *J. Amer. Chem. Soc.*, 1936, **58**, 1738.
[4] Bell and Kenyon, *J.*, 1926, 3044.

of the ether was followed by addition of dioxan (100 c.c.), freshly prepared silver oxide (1 g.), and dioxan saturated with ammonia (100 c.c.). The suspension was stirred and heated at 80—100° for 3 hr., filtered, and evaporated to give micro-crystals, m. p. 169—175° (0·95 g.). Repeated recrystallisation from aqueous alcohol gave long white needles of *4-methoxy-3-diphenylylacetamide*, m. p. 180·5° (Found: C, 74·7; H, 6·5; N, 5·7. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·6; N, 5·8%). Hydrolysis with alcoholic potassium hydroxide, and recrystallisation from aqueous alcohol, then from benzene–light petroleum (b. p. 60—80°) gave white needles, m. p. 170—171°, of *4-methoxy-3-diphenylylacetic acid* (Found: C, 74·2; H, 5·9%; equiv., 239·4. $C_{15}H_{14}O_2$ requires C, 74·4; H, 5·8%; equiv., 242·3). The *p-bromphenacyl ester* formed white micro-crystals (from alcohol), m. p. 131° (Found: C, 62·7; H, 4·4; Br, 18·0. $C_{24}H_{21}O_4Br$ requires C, 62·9; H, 4·4; Br, 18·2%).

SCHOOL OF PHARMACY, UNIVERSITY OF LONDON. [*Received, September 10th*, 1957.]

## 180. *Thermogravimetric Analysis of Ammonium Phosphomolybdate in vacuo.*

By S. J. GREGG and R. STOCK.

As a preliminary to the experimental study of the adsorptive properties [1] of ammonium phosphomolybdate it was necessary to ascertain the stability of the substance towards heat. Accordingly it was subjected to thermogravimetric analysis *in vacuo* in two stages by means of an electromagnetic sorption balance [2] connected through a liquid-oxygen trap to mercury-condensation and rotary pumps: the sample was first maintained at 180° till further loss in weight was negligible and was then raised in temperature at a rate of 1·2° per minute to 630°, after which it was rapidly heated to 830°.

The loss in weight at 180° was only 0·4%, probably due to adsorbed water since the trap contained no ammonia or nitric acid. Above 180° the rate of loss gradually increased to *ca.* 380°, when it sharply increased up to 470°, and then slowed down till 630° was reached (except for a curious notch in the curve at 540°, also reported by Duval [3] during thermogravimetric analysis in air); above this temperature the loss again accelerated and at 800° became too rapid to measure accurately.

The loss in weight between 180° and 470° was 6·60%, *i.e.*, 2·41% *in excess* of that to be expected for the reaction

$$(NH_4)_3PO_4,12MoO_3 \longrightarrow \tfrac{1}{2}P_2O_5,24MoO_3 + 3NH_3 + 1\tfrac{1}{2}H_2O \quad . \quad . \quad . \quad . \quad . \quad (1)$$

but the ammonia found in the contents of the trap corresponded to only 1·17%, *i.e.*, 1·55% *less than* the amount required by equation (1). The two discrepancies are accounted for by postulating that the " lost " ammonia has been oxidised by the $MoO_3$:

$$2NH_3 + 3O \text{ (from the } MoO_3) \longrightarrow 3H_2O + N_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

the 1·55% of ammonia would by this equation withdraw 2·20% of oxygen from the solid, which would be registered as an additional loss in weight; and this figure agrees within experimental error with the 2·41% found by experiment. The reduction of the solid is confirmed by the formation of a blue sublimate on the inside of the tube of the balance " case " just above the furnace.

Since the loss of weight between 180° and 380° (1·45%) was within experimental limits equal to that calculated for the loss of $1NH_3 + 0{\cdot}5H_2O$ (1·40%), the reduction only sets in above 380°.

The ammonium phosphomolybdate was prepared by addition of a solution of ammonium molybdate containing ammonium and nitrate ions to potassium dihydrogen phosphate at 50°, following the detailed procedure of Thistlethwaite.[4]

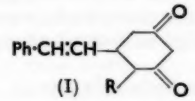
THE WASHINGTON SINGER LABORATORIES,
THE UNIVERSITY, EXETER. [*Received, October 14th*, 1957.]

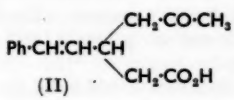
[1] Gregg and Stock, *Trans. Faraday Soc.*, 1957, **53**, 1355.
[2] Gregg, *J.*, 1955, 1498.
[3] Duval, " Thermogravimetric Analysis," Elsevier, Amsterdam, 1953, p. 130.
[4] Thistlethwaite, *Analyst*, 1947, **72**, 531.

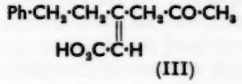
## 181. cyclo*Hexane*-1 : 3-*diones. Part III.* Alkaline Hydrolysis of Ethyl* 2 : 4-*Dioxo*-6-*styryl*cyclo*hexanecarboxylate.*

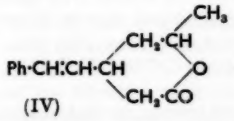
By G. R. Ames and W. Davey.

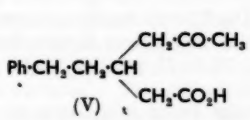
In Part I [1] of this series, it was shown that hydrolysis of ethyl 2 : 4-dioxo-6-styryl*cyclo*hexanecarboxylate (I; R = $CO_2Et$) with hydrochloric acid did not yield the expected 5-oxo-3-styrylhexanoic acid (II), but gave instead the isomeric compound *trans*-5-oxo-3-phenethylhex-2-enoic acid (III), m. p. 127—128°. We have now found that when the dione-ester (I; R = $CO_2Et$) is refluxed with barium hydroxide solution, there is obtained a new acid, m. p. 89—90°, which, on evidence given below, is assigned structure (II). Ozonolysis of this acid gave benzaldehyde as the only steam-volatile product. The ultraviolet absorption spectrum of the new acid ($\lambda_{max.}$ 249·5 mμ; ε 19,500) was characteristic of a compound containing the styryl chromophore.[2] The infrared spectrum (in Nujol) contains a band at 1688 cm.$^{-1}$ (unconjugated acids [3] absorb at 1689—1754 cm.$^{-1}$; the acid (III) shows a band at 1679 cm.$^{-1}$); there is also a shoulder (1703 cm.$^{-1}$) due to the ketone group, and a band (970 cm.$^{-1}$) caused by the *trans* –CH=CH– system.[4]

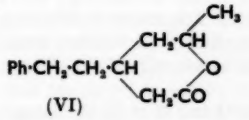

(I)


(II)


(III)


(IV)


(V)


(VI)

The esters of δ-keto-acids are cyclised by sodium alkoxides to *cyclo*hexane-1 : 3-diones.[5] Treatment of the methyl ester of the acid (II) with sodium methoxide yielded 5-styryl-*cyclo*hexane-1 : 3-dione (I; R = H). This observation confirms the assignment of structure (II).

Treatment of the acid (II) with potassium borohydride afforded the lactone (IV), which yielded benzaldehyde on ozonolysis. When the acid (II) was hydrogenated (palladised charcoal), 1 mol. of hydrogen was absorbed; the product, 5-oxo-3-phenethylhexanoic acid (V), was shown, by comparison of the 2 : 4-dinitrophenylhydrazones, to be identical with that obtained previously [1] by hydrolysis of ethyl 2 : 4-dioxo-6-phenethyl*cyclo*hexanecarboxylate. Hydrogenation of the acid (II) with a Raney nickel W7 catalyst gave the saturated lactone (VI); this is in contrast to the αβ-unsaturated acid (III), in which the double bond is not reduced under these conditions.[1] Attempts to prepare 3-styrylhexanoic acid by reduction of the keto-acid (II) by the Wolff–Kishner and the Clemmensen method were unsuccessful, as no crystalline product could be isolated. An attempt to isomerise the acid (II) by treatment with hydrochloric acid under the conditions used for the preparation of the acid (III), also yielded an uncrystallisable product.

*Experimental.*—Ultraviolet absorption spectra were determined for EtOH solutions, using a Unicam S.P. 500 spectrophotometer.

*5-Oxo-3-styrylhexanoic acid* (II). Ethyl 2 : 4-dioxo-6-styryl*cyclo*hexanecarboxylate (50 g.) and barium hydroxide (120 g.) in water (2·5 l.) were refluxed together for 20 hr. The mixture was acidified and decanted from an oil. Gradually *5-oxo-3-styrylhexanoic acid* (16 g.) separated;

* Part II, *J.*, 1957, 3480.

[1] Ames and Davey, *J.*, 1956, 3001.
[2] Overberger and Tanner, *J. Amer. Chem. Soc.*, 1955, **77**, 369.
[3] Randall, Fowler, Fuson, and Dangl, "Infrared Determination of Organic Structures," Van Nostrand, New York, 1949, p. 20.
[4] Bellamy, "Infrared Spectra of Complex Molecules," Methuen, London, 1954, p. 31.
[5] Vorländer, *Annalen*, 1896, **294**, 253.

it formed prisms, m. p. 89—90°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 72·2; H, 6·9. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%). The *semicarbazone*, prisms from ethyl acetate, had m. p. 165° (decomp.) (Found: C, 61·8; H, 6·5. $C_{15}H_{19}O_3N_3$ requires C, 62·3; H, 6·6%), and the *methyl ester* had b. p. 160—162°/1·2 mm., $n_D^{21}$ 1·5353 (Found: C, 73·4; H, 7·5. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%).

*Cyclisation of methyl 5-oxo-3-styrylhexanoate.* The foregoing ester (2·9 g.) was added to a solution of sodium (0·3 g.) in methanol (50 c.c.) and the mixture refluxed for 3 hr. The solution was concentrated, diluted with water, and then washed with ether to remove any unchanged ester. Acidification of the aqueous layer afforded 5-styryl*cyclo*hexane-1 : 3-dione (1 g.), m. p. and mixed m. p. 183—184°.

*5-Hydroxy-3-styrylhexanoic lactone* (IV). A solution of 5-oxo-3-styrylhexanoic acid (3 g.) and potassium borohydride (6 g.) in water (100 c.c.) was set aside overnight. The mixture was acidified and the product isolated with ether. Distillation gave the *lactone* (2·6 g.), b. p. 188°/1·5 mm., $n_D^{26}$ 1·5676 (Found: C, 77·6; H, 7·5. $C_{14}H_{16}O_2$ requires C, 77·7; H, 7·5%), which solidified on storage, having m. p. 54—55°, $\lambda_{max.}$ 250·5 mμ (ε 19,400), and infrared bands at 968 and 1721 cm.$^{-1}$ (in Nujol; 1726 cm.$^{-1}$ in $CHCl_3$).

*Hydrogenation of 5-oxo-3-styrylhexanoic acid.* (*a*) The acid (3 g.) in ethanol (150 c.c.) was shaken under hydrogen with 5% palladised charcoal (1 g.). Uptake of hydrogen ceased when 325 c.c. had been absorbed (1 mol.; 295 c.c.). The catalyst was removed, the solution evaporated, and the oily residue treated with Brady's reagent. The 2 : 4-dinitrophenylhydrazone thus obtained was identical (m. p. and mixed m. p. 147—148°) with that of 5-oxo-3-phenethylhexanoic acid (V) obtained previously.[1]

(*b*) A mixture of the acid (4 g.) in ethanol (150 c.c.), 2N-sodium hydroxide (20 c.c.), and Raney nickel (about 5 g.) was shaken under hydrogen until absorption ceased (vol. absorbed, 720 c.c.; $2H_2$ requires 780 c.c.). The filtered liquid was concentrated and then acidified, and the product was isolated with ether. *5-Hydroxy-3-phenethylhexanoic lactone* (VI) had b. p. 164°/0·5 mm., $n_D^{22}$ 1·5311 (Found: C, 77·3; H, 8·6. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%).

We thank Miss E. M. Tanner, Parke, Davis & Co., Hounslow, Middlesex, for determining the infrared spectra and for helpful suggestions on their interpretation.

THE POLYTECHNIC, 309 REGENT ST., LONDON, W.1. [*Received, November 4th*, 1957.]

---

## 182. *Action of Acidic Reagents on 2 : 4 : 5-Trimethoxybenzyl and 2-Methoxy-4 : 5-methylenedioxybenzyl Alcohol.*

By T. R. GOVINDACHARI, K. NAGARAJAN, and P. C. PARTHASARATHY.

ALTHOUGH Harley-Mason and Jackson [1] noted the formation of a chlorine-free compound, m. p. 101°, by the action of thionyl chloride on 2 : 4 : 5-trimethoxybenzyl alcohol, its structure was not elucidated. During other work in this laboratory, it was found that the compound was formed from the alcohol in nearly quantitative yield by the action of thionyl chloride in chloroform or pyridine, of hydrogen chloride in benzene, or of aqueous 4N-hydrochloric acid. With the last reagent it was possible to demonstrate the formation of *ca.* 1 mol. of formaldehyde. Analyses suggested that the compound was 2 : 4 : 5 : 2′ : 4′ : 5′-hexamethoxydiphenylmethane. This was confirmed by comparison with a specimen synthesised as follows: 1 : 2 : 4-Trimethoxybenzene, in Friedel–Crafts reaction at 0—5° with 2 : 4 : 5-trimethoxybenzoyl chloride, gave a benzophenone which was reduced to the diphenylmethane derivative by hydrogen and pallidised charcoal in acetic acid containing perchloric acid. (Friedel–Crafts reaction at 70—80° gave 2 : 4 : 5 : 2′ : 4′ : 5′-hexamethoxydiphenyl.[2])

2-Methoxy-4 : 5-methylenedioxybenzyl alcohol likewise yielded 2 : 2′-dimethoxy-4 : 5—4′ : 5′-bismethylenedioxydiphenylmethane on treatment with thionyl chloride in the cold.

[1] Harley-Mason and Jackson, *J.*, 1954, 1168.
[2] Taylor, *J.*, 1954, 2636.

*Experimental.*—Ultraviolet measurements are for 95% ethanol solutions.

2 : 4 : 5-*Trimethoxybenzyl alcohol.* Asarylaldehyde (5 g.) in tetrahydrofuran (40 ml.) was added to a stirred suspension of lithium aluminium hydride (1·5 g.) in ether (30 ml.). Next morning the mixture was decomposed with water. The ether–tetrahydrofuran layer was decanted, dried, and evaporated. Crystallisation of the residue (4·5 g.) from light petroleum (b. p. 40—60°) gave 2 : 4 : 5-trimethoxybenzyl alcohol, plates, m. p. 73° (Harley-Mason *et al.*[1] report m. p. 70—71°).

2 : 4 : 5 : 2′ : 4′ : 5′-*Hexamethoxydiphenylmethane.* The foregoing alcohol (4·5 g.) in benzene (50 ml.) was treated with dry hydrogen chloride in the cold and left overnight. Next morning, the benzene solution was washed successively with water and aqueous sodium carbonate. Evaporation of the solvent left a solid (3·6 g.) which crystallised from aqueous alcohol as needles, m. p. and mixed m. p. 102° with 2 : 4 : 5 : 2′ : 4′ : 5′-hexamethoxydiphenylmethane, $\lambda_{max.}$ 290 mμ (log ε 3·93) (Harley-Mason *et al.*[1] report m. p. 101°) (Found: C, 65·5, 65·7; H, 6·8, 6·8; OMe, 50·5. Calc. for $C_{19}H_{24}O_6$: C, 65·5; H, 6·9; 6OMe, 53·4%).

2 : 4 : 5 : 2′ : 4′ : 5′-*Hexamethoxydiphenyl.* 2 : 4 : 5-Trimethoxybenzoyl chloride (1 g.) in benzene (40 ml.) containing 1 : 2 : 4-trimethoxybenzene (1·5 g.) was treated with aluminium chloride (1 g.) in small lots, then heated at 80° for 1 hr. and worked up as usual, the diphenyl (0·5 g.) being obtained as needles (from acetic acid), m. p. and mixed m. p. 178° with a synthetic specimen.[2]

2 : 4 : 5 : 2′ : 4′ : 5′-*Hexamethoxybenzophenone.* The foregoing reaction at 0—5° with carbon disulphide as solvent gave 2 : 4 : 5 : 2′ : 4′ : 5′-hexamethoxybenzophenone as lemon-yellow tablets (from methanol), m. p. 150—151° (Oskoläs[3] obtained it as a secondary product from 1 : 2 : 4-trimethoxybenzene and oxalyl chloride containing aluminium chloride and reported m. p. 147°).

2 : 4 : 5 : 2′ : 4′ : 5′-*Hexamethoxydiphenylmethane.* The foregoing benzophenone (0·2 g.) in acetic acid (10 ml.) containing 70% perchloric acid (0·2 ml.) was reduced (1 hr.) with hydrogen at 1 atm. at 50—60°, in presence of 5% palladised charcoal (0·2 g.). The catalyst was filtered off, and the filtrate concentrated *in vacuo*. The oily residue was taken up in ether, washed with water and dried ($Na_2SO_4$). Evaporation of the solvent gave 2 : 4 : 5 : 2′ : 4′ : 5′-hexamethoxydiphenylmethane (0·1 g.), needles (from alcohol), m. p. 102° (Found: C, 65·3; H, 6·7%).

2-*Methoxy*-4 : 5-*methylenedioxybenzyl alcohol.* Reduction of 2-methoxy-4 : 5-methylenedioxybenzaldehyde[4] (1 g.) by lithium aluminium hydride (1 g.) in ether (30 ml.) yielded 2-*methoxy*-4 : 5-*methylenedioxybenzyl alcohol*, needles (from light petroleum), m. p. 54—55° (Found: C, 59·2; H, 5·2. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%).

2 : 2′-*Dimethoxy*-4 : 5-4′ : 5′-*bismethylenedioxydiphenylmethane.* The foregoing alcohol (0·5 g.) in chloroform (5 ml.) with thionyl chloride (1 ml.) in the cold gave 2 : 2′-*dimethoxy*-4 : 5-4′ : 5′-*bismethylenedioxydiphenylmethane* (0·3 g.), needles (from alcohol), m. p. 140—141°, $\lambda_{max.}$ 301 mμ (log ε 3·97) (Found: C, 64·8; H, 5·3. $C_{17}H_{14}O_6$ requires C, 64·6; H, 5·1%).

We thank the Government of India for a senior research scholarship (to P. C. P.), and Mr. S. Selvavinayakam for analyses.

PRESIDENCY COLLEGE, MADRAS, INDIA. [*Received, November 12th*, 1957.]

[3] Oskoläs, *Acta Lit. Sci. Univ. Hung. Francisco-Josephinae, Sect. chem., min., phys.*, 1932, **2**, 165; *Chem. Abs.*, 1933, **27**, 1874.

[4] Campbell, Hopper, and Campbell, *J. Org. Chem.*, 1951, **16**, 1736.

---

## 183. *Polynuclear Heterocyclic Systems. Part XII.* Further Examples of the Elbs Reaction with Heterocyclic Ketones.*

By G. M. BADGER and B. J. CHRISTIE.

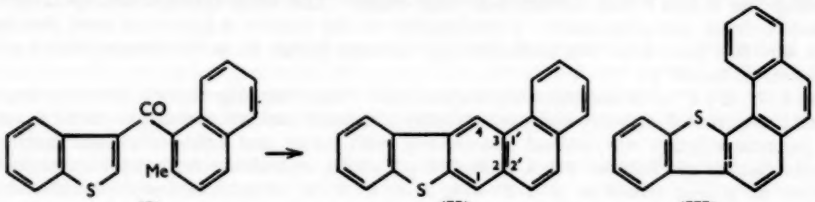
PYROLYSIS of 3-*o*-toluoylthionaphthen has been shown[1] to give 9-thia-1 : 2-benzofluorene and not the expected 9-thia-2 : 3-benzofluorene, and a possible mechanism for the rearrangement was advanced.[2] We now find that two analogues, (I) and (IV), are not rearranged in similar reactions.

* Part XI, *J.*, 1956, 3438.

[1] Badger and Christie, *J.*, 1956, 3435.

[2] Tilak, *Proc. Indian Acad. Sci.*, 1951, **33**, *A*, 131.

Cyclodehydration of 3-(2-methyl-1-naphthoyl)thionaphthen (I) occurred very readily, giving a good yield of product: if this had structure (II), it should give a 1 : 4-quinone on oxidation; if it had structure (III) it would give a 1 : 2-quinone. Chromic acid oxidation




(I) (II) (III)

of the product gave the known 1 : 4-quinone.[2] The product is therefore (II) and this is confirmed by the ultraviolet absorption spectrum, resembling that of 1 : 2-7 : 8-dibenzanthracene, with which it is isoelectronic[3] (Fig. 1).

FIG. 1. FIG. 2.

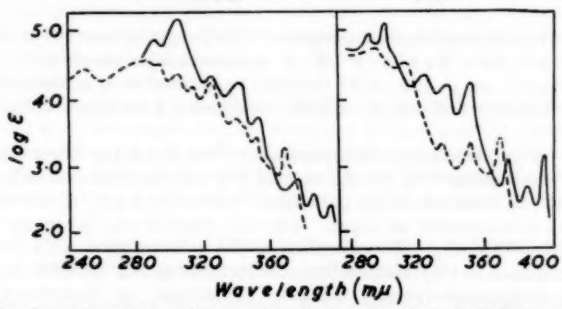
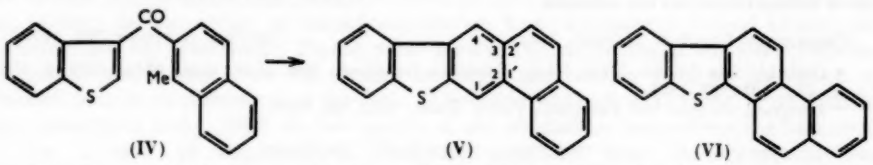



FIG. 1. *Ultraviolet absorption spectra of* (– – – –) *9-thianaphtho*(2′ : 1′-2 : 3)*fluorene* (II) *in* 95% EtOH *and of* (———) 1 : 2-7 : 8-*dibenzanthracene in* $C_6H_6$.[4]

FIG. 2. *Ultraviolet absorption spectra of* (– – – –) *9-thianaphtho*(1′ : 2′-2 : 3)*fluorene* (V) *in* $C_6H_6$ *and of* (———) 1 : 2-5 : 6-*dibenzanthracene in* $C_6H_6$.[4]

Cyclodehydration of 3-(1-methyl-2-naphthoyl)thionaphthen (IV) also proceeded readily, giving a product oxidised to a 1 : 4-quinone[2] and therefore having structure (V) and not (VI). The absorption spectrum resembles that of 1 : 2-5 : 6-dibenzanthracene, with which it is isoelectronic (Fig. 2).




(IV) (V) (VI)

Rearrangement during pyrolysis of 3-acylthionaphthens is thus not a general characteristic.

*Experimental.*—*2-Methyl-1-naphthoic acid.* Carboxylation of 2-methyl-1-naphthylmagnesium bromide with anhydrous carbon dioxide[5] gave 2-methyl-1-naphthoic acid (71% yield), needles, m. p. 126—127° (from benzene), which was converted into the acid chloride in quantitative yield with excess of thionyl chloride.

*3-(2-Methyl-1-naphthoyl)thionaphthen.* Stannic chloride (27 g.) in thiophen-free benzene (75 c.c.) was added during 30 min., at room temperature, to a stirred solution of thionaphthen

[3] Badger and Christie, *J.*, 1956, 3438.
[4] Clar, " Aromatische Kohlenwasserstoffe," Springer-Verlag, Berlin, 2nd edn., 1952.
[5] Cf. Adams and Binder, *J. Amer. Chem. Soc.*, 1941, **63**, 2773.

(13·5 g.) and 2-methyl-1-naphthoyl chloride (20 g.) in thiophen-free benzene (200 c.c.). After refluxing for 3 hr. the mixture was poured on ice and hydrochloric acid. The benzene layer was washed with 10% hydrochloric acid, water, 10% aqueous sodium hydroxide, and water, dried ($Na_2SO_4$), and evaporated. The resulting 3-(2-*methyl*-1-*naphthoyl*)*thionaphthen* (24 g., 80%) crystallised from hexane in prisms, m. p. 160—161° (Found: C, 79·7; H, 4·75; S, 10·8. $C_{20}H_{14}OS$ requires C, 79·4; H, 4·7; S, 10·6%). It did not form a 2 : 4-dinitrophenylhydrazone or an oxime, but showed carbonyl absorption at 1639 cm.$^{-1}$.

9-*Thianaphtho*(2′ : 1′-2 : 3)*fluorene*. The above ketone (10 g.) was heated under reflux (bath-temp., 450°) for 3 hr., by which time evolution of water had ceased. A small amount of 2-methylnaphthalene was distilled off and characterised as the picrate, m. p. and mixed m. p. 115°. The residue was chromatographed in benzene on alumina. Elution with benzene, followed by evaporation and recrystallisation of the *product* from ethanol, gave leaflets (5·1 g., 54%), m. p. 141—142° (Found: C, 84·55; H, 4·3; S, 11·2. $C_{20}H_{12}S$ requires C, 84·5; H, 4·25; S, 11·3%). Its *dipicrate* crystallised from benzene in orange-red needles, m. p. 176—177° (Found: C, 52·0; H, 2·7; N, 10·9. $C_{32}H_{18}O_{14}N_6S$ requires C, 51·8; H, 2·4; N, 11·3%).

Chromium trioxide (0·3 g.) in water (10 c.c.) was added to a boiling solution of the above thiafluorene (0·2 g.) in glacial acetic acid (25 c.c.), and the mixture refluxed for 30 min. Pouring the whole into water gave an orange solid which was chromatographed in benzene on alumina. Recrystallisation from benzene gave the quinone as orange needles, m. p. 260—261°, recovered unchanged after being heated with *o*-phenylenediamine (Found: C, 76·35; H, 3·4; S, 10·3. Calc. for $C_{20}H_{10}O_2S$: C, 76·4; H, 3·2; S, 10·2%). Tilak [2] gives m. p. 261—262·5°.

1-*Methyl*-2-*naphthoic acid*. Cyclisation of ethyl α-phenethylacetoacetate (10 g.) with concentrated sulphuric acid (200 c.c.) at room temperature gave 3 : 4-dihydro-1-methyl-2-naphthoic acid (6 g., 75%) and not the fully aromatic compound as found by von Auwers and Möller.[6] It formed needles (from benzene), m. p. 127° (lit.,[6] 127°). Dehydrogenation was effected by 12 hours' refluxing with 10% palladium–charcoal in *p*-cymene. The resulting 1-methyl-2-naphthoic acid, m. p. 177—178° (lit.,[6] 177—178°), was converted into the acid chloride with excess of thionyl chloride.

3-(1-*Methyl*-2-*naphthoyl*)*thionaphthen*. Stannic chloride (9 g.) in thiophen-free benzene (30 c.c.), thionaphthen (4 g.), and 1-methyl-2-naphthoyl chloride (6 g.) in thiophen-free benzene, gave, as above, 3-(1-*methyl*-2-*naphthoyl*)*thionaphthen* (5·5 g., 61%), needles (from hexane), m. p. 119—120° (Found: C, 79·6; H, 4·7; S, 10·7%), $\nu_{max.}$ 1639 cm.$^{-1}$ (C=O).

9-*Thianaphtho*(1′ : 2′-2 : 3)*fluorene*. The above ketone (3 g.) was heated under reflux (bath-temp., 450°) for 4½ hr. The *product* (1·2 g., 43%) separated from benzene in needles, m. p. 322—323° (Found: C, 84·8; H, 4·2; S, 11·3%), and gave the 1 : 4-quinone, red needles (from benzene), m. p. 256° (lit.,[2] m. p. 255—256°), recovered unchanged after treatment with *o*-phenylenediamine.

Ultraviolet absorption spectra were determined with a Hilger Uvispek Spectrophotometer.

Microanalyses were carried out by the C.S.I.R.O. Microanalytical Laboratory, Melbourne. We also thank Dr. H. J. Rodda and Mr. A. G. Moritz for the infrared spectra. One of us (B. J. C.) has been working with an I.C.I.A.N.Z. Fellowship.

UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA. [*Received, September 16th*, 1957.]

[6] von Auwers and Möller, *J. prakt. Chem.*, 1925, **109**, 124.

---

## 184. *Ethoxide–Hydroxide-ion Competition in Bimolecular Nucleophilic Substitutions in Alkaline Aqueous Ethyl Alcohol.*

By Y. POCKER.

IN the earlier investigation [1] of the reactions of *iso*propyl bromide in aqueous ethyl alcohol, the full amount of ethyl *iso*propyl ether formed under bimolecular conditions was possibly not revealed because of the difficulty of isolating products from the very dilute solutions used to obtain kinetic conditions. From a large-scale product analysis (*ca.* 4 l. of reaction mixture) it has now been possible to isolate, after the complete decomposition of *iso*propyl bromide in strongly alkaline 60% aqueous ethyl alcohol, an amount of ethyl *iso*propyl ether corresponding to 23·8 moles % of the total organic products.

[1] Hughes, Ingold, and Shapiro, *J.*, 1936, 225.

An independent check has shown that the recovery was 68%, indicating that under the above conditions the amount of ethyl *iso*propyl ether actually formed is *ca.* 35 moles % of the total organic products.

From the data given by Hughes, Ingold, and Shapiro [1] it is possible to show that, under the conditions used, the unimolecular reaction amounts to 4% and the total bimolecular reaction ($S_N2 + E2$) to 96%. The latter value comprises 55% of bimolecular elimination ($E2$) and 41% of bimolecular substitution ($S_N2$).

The amount of ethyl *iso*propyl ether formed under unimolecular conditions is not known but cannot be larger than that formed in the total unimolecular reaction. When the total amount of ethyl *iso*propyl ether formed in the reaction is corrected for this relatively small uncertainty one finds that $33 \pm 2\%$ of the total bimolecular reaction ($S_N2 + E2$) results in the formation of ether. This result means that *ca.* $80 \pm 5\%$ of the bimolecular substitution represents replacement of bromide by ethoxide ion.

Under the conditions used, the rate of bimolecular ethoxylation is thus about four times that of bimolecular hydroxylation. The relative anion concentrations $[EtO^-] : [OH^-]$ and the ratio of the corresponding second-order rate coefficients $k_2^{EtOH^-} : k_2^{OH^-}$, jointly contribute to this result, *i.e.*:

$$\left(\frac{\text{Ethoxylation rate}}{\text{Hydroxylation rate}}\right)_{S_N2} = \frac{[OEt^-]}{[OH^-]} \cdot \frac{k_2^{OEt^-}}{k_2^{OH^-}}$$

In the absence of a precise value for the equilibrium, $OH^- + EtOH = EtO^- + H_2O$, in 60% aqueous ethyl alcohol at 70°, the concentration ratio cannot be treated separately from the ratio of the corresponding second-order rate coefficients.

In conclusion, it should be noted that variations in temperature or solvent composition will change the above concentration ratio of ethoxide to hydroxide ions and thereby affect also the wider issue of bimolecular rates of substitution and elimination.

*Experimental.—Materials.* *iso*Propyl bromide (B.D.H.) was dried with phosphoric oxide and fractionated, the fraction of b. p. 60°/760 mm. being used for measurements. Commercial absolute ethyl alcohol was dried over lime and fractionated. The 60% aqueous ethyl alcohol was made by mixing 3 volumes of this absolute alcohol with 2 volumes of water.

*Product analysis.* (*a*) Isolation experiment. The reaction mixture comprising absolute ethyl alcohol (2·4 l.) water (1·6 l.), "AnalaR" sodium hydroxide (320 g.), and *iso*propyl bromide (400 g.) was heated in sealed bulbs for 10 hr. at 70°, then fractionated. The fraction boiling below 58° was collected, the remaining mixture diluted with water (4 vols.) and fractionated again, the fraction boiling below 58° collected. The mixed fractions were dried over potassium and distilled from it, yielding 70 g. of pure ethyl *iso*propyl ether, b. p. 54° (Found: C, 68·4; H, 13·6. Calc. for $C_5H_{12}O$: C, 68·1; H, 13·7%). A second experiment gave 66 g. of ether, b. p. 54° (mean, 68 g., 23·8 moles %).

(*b*) Recovery experiment. Absolute ethyl alcohol (2·4 l.), water (1·6 l.), and ethyl *iso*propyl ether (59 g.) were heated in sealed bulbs for 4 hr. at 70°, then treated as described above, affording 39 g. of pure ethyl *iso*propyl ether, b. p. 54°, *i.e.*, 66% recovery. A second experiment with 60 g. of ether gave 70% recovery.

The author is indebted to Professors E. D. Hughes, F.R.S., and C. K. Ingold, F.R.S., for much valued advice, and to Mr. T. Collins for technical assistance.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER ST., LONDON, W.C.1. [*Received, October 9th*, 1957.]